PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 19 June 2001 (19.06.01)	
International application No. PCT/NL00/00603	**Applicant's or agent's file reference** P49634PC00
International filing date (day/month/year) 30 August 2000 (30.08.00)	**Priority date** (day/month/year) 30 August 1999 (30.08.99)
Applicant VAN SCHIJNDEL, Renée, Josie, Gide et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

14 March 2001 (14.03.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740 14 35

Authorized officer

Zakaria EL KHODARY

Telephone No.: (41-22) 338 83 38

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

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PCT/NL 00 / 00603
International Application No.

30 AUG 2000 (30.08.00)
International Filing Date

BUREAU VOOR DE INDUSTRIËLE EIGENDOM
PCT. INTERNATIONAL APPLICATION

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) P49634PC00

Box No. I TITLE OF INVENTION

Immobilization of active substances

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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☐ This person is also inventor.

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Teleprinter No.

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State *(that is, country)* of residence: NL

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

van Schijndel, Renée Josie Gide
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This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

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This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Mr Ir A.W. Prins, c.s.

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Teleprinter No.

☐ **Adress for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: NL

State *(that is, country)* of residence: NL

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: NL

State *(that is, country)* of residence: NL

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: NL

State *(that is, country)* of residence: NL

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Δ See #08

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

LENSELINK, Willem Δ

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: NL

State *(that is, country)* of residence: NL

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☒ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **MZ** Mozambique, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☒ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ **AE** United Arab Emirates
☒ **AG** Antigua and Barbuda
☒ **AL** Albania .....
☒ **AM** Armenia .....
☒ **AT** Austria .....
☒ **AU** Australia .....
☒ **AZ** Azerbaijan
☒ **BA** Bosnia and Herzegovina .....
☒ **BB** Barbados
☒ **BG** Bulgaria .....
☒ **BR** Brazil .....
☒ **BY** Belarus .....
☒ **BZ** Belize
☒ **CA** Canada
☒ **CH and LI** Switzerland and Liechtenstein
☒ **CN** China .....
☒ **CR** Costa Rica .....
☒ **CU** Cuba .....
☒ **CZ** Czech Republic .....
☒ **DE** Germany .....
☒ **DK** Denmark .....
☒ **DM** Dominica
☒ **DZ** Algeria .....
☒ **EE** Estonia .....
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☒ **GE** Georgia .....
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☒ **GM** Gambia
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☒ **ID** Indonesia
☒ **IL** Israel .....
☒ **IN** India .....
☒ **IS** Iceland
☒ **JP** Japan .....
☒ **KE** Kenya .....
☒ **KG** Kyrgyzstan .....
☒ **KP** Democratic People's Republic of Korea .....
☒ **KR** Republic of Korea .....
☒ **KZ** Kazakhstan .....
☒ **LC** Saint Lucia
☒ **LK** Sri Lanka
☒ **LR** Liberia
☒ **LS** Lesotho .....
☒ **LT** Lithuania
☒ **LU** Luxembourg
☒ **LV** Latvia
☒ **MA** Morocco .....
☒ **MD** Republic of Moldova .....
☒ **MG** Madagascar .....
☒ **MK** The former Yugoslav Republic of Macedonia .....
☒ **MN** Mongolia
☒ **MW** Malawi .....
☒ **MX** Mexico .....
☒ **MZ** Mozambique
☒ **NO** Norway
☒ **NZ** New Zealand .....
☒ **PL** Poland .....
☒ **PT** Portugal .....
☒ **RO** Romania
☒ **RU** Russian Federation .....
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☒ **SI** Slovenia .....
☒ **SK** Slovakia .....
☒ **SL** Sierra Leone .....
☒ **TJ** Tajikistan .....
☒ **TM** Turkmenistan .....
☒ **TR** Turkey .....
☒ **TT** Trinidad and Tobago .....
☒ **TZ** United Republic of Tanzania
☒ **UA** Ukraine .....
☒ **UG** Uganda .....
☒ **US** United States of America .....
☒ **UZ** Uzbekistan .....
☒ **VN** Viet Nam .....
☒ **YU** Yugoslavia .....
☒ **ZA** South Africa .....
☒ **ZW** Zimbabwe .....

Check-box reserved for designating States which have become party to the PCT after issuance of this sheet:

☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

See Notes to the request form

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 30 August 1999 (30.08.99)	1012933	NL		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s) 1

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*: ISA / EP

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date (day/month/year)	Number	Country (or regional Office)
16 May 2000	SN 33790 NL	NL

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	: 4
description (excluding sequence listing part)	: 18
claims	: 3
abstract	: 1
drawings	: 5
sequence listing part of description	:
Total number of sheets	: 31

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological materia
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

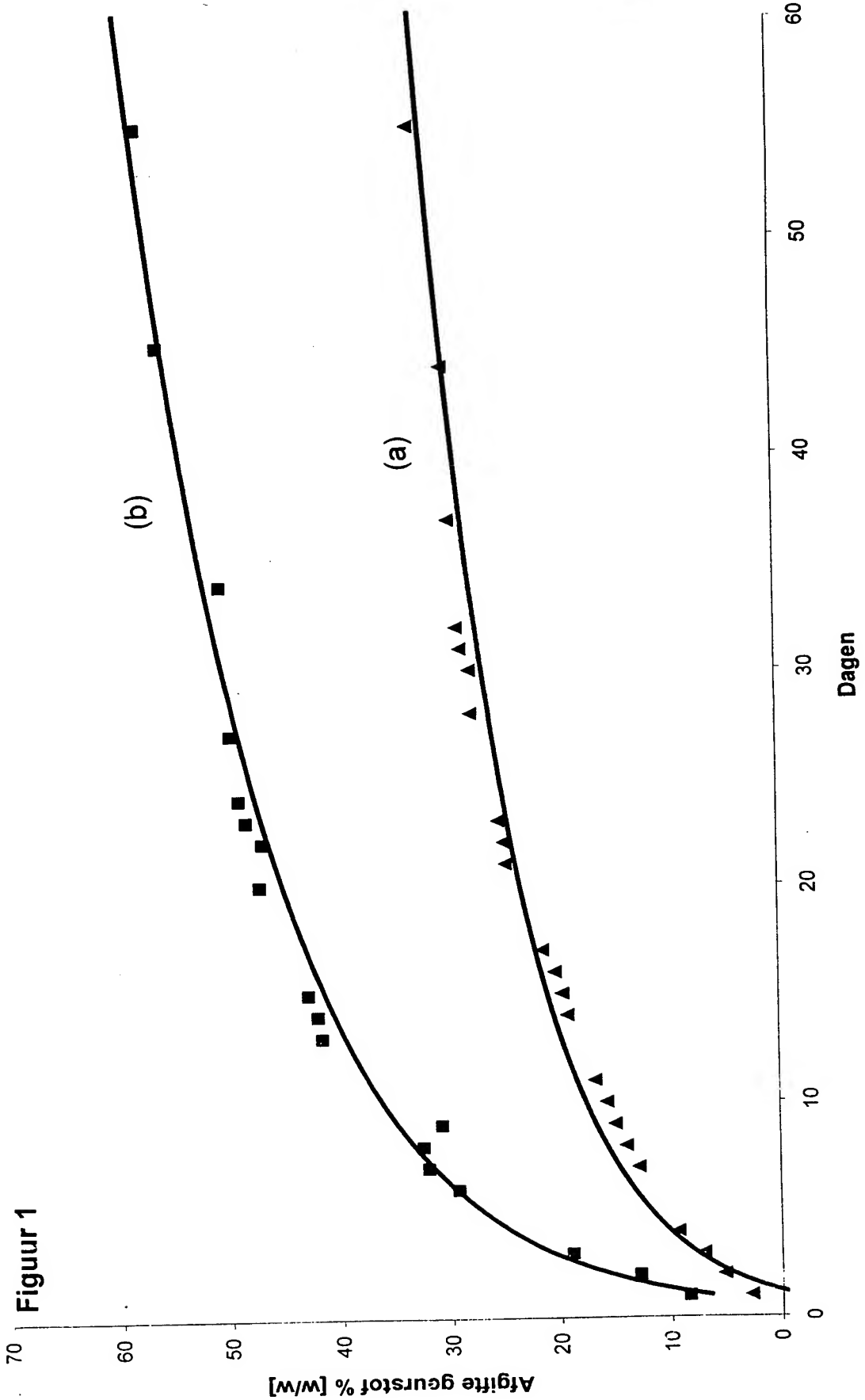
M J. Harzmann

For receiving Office use only

1. Date of actual receipt of the purported international application: 30 AUG 2000 (30.08.00)
2. Drawings: ☒ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau: 06 OCTOBER 2000 (06 OCT 2000)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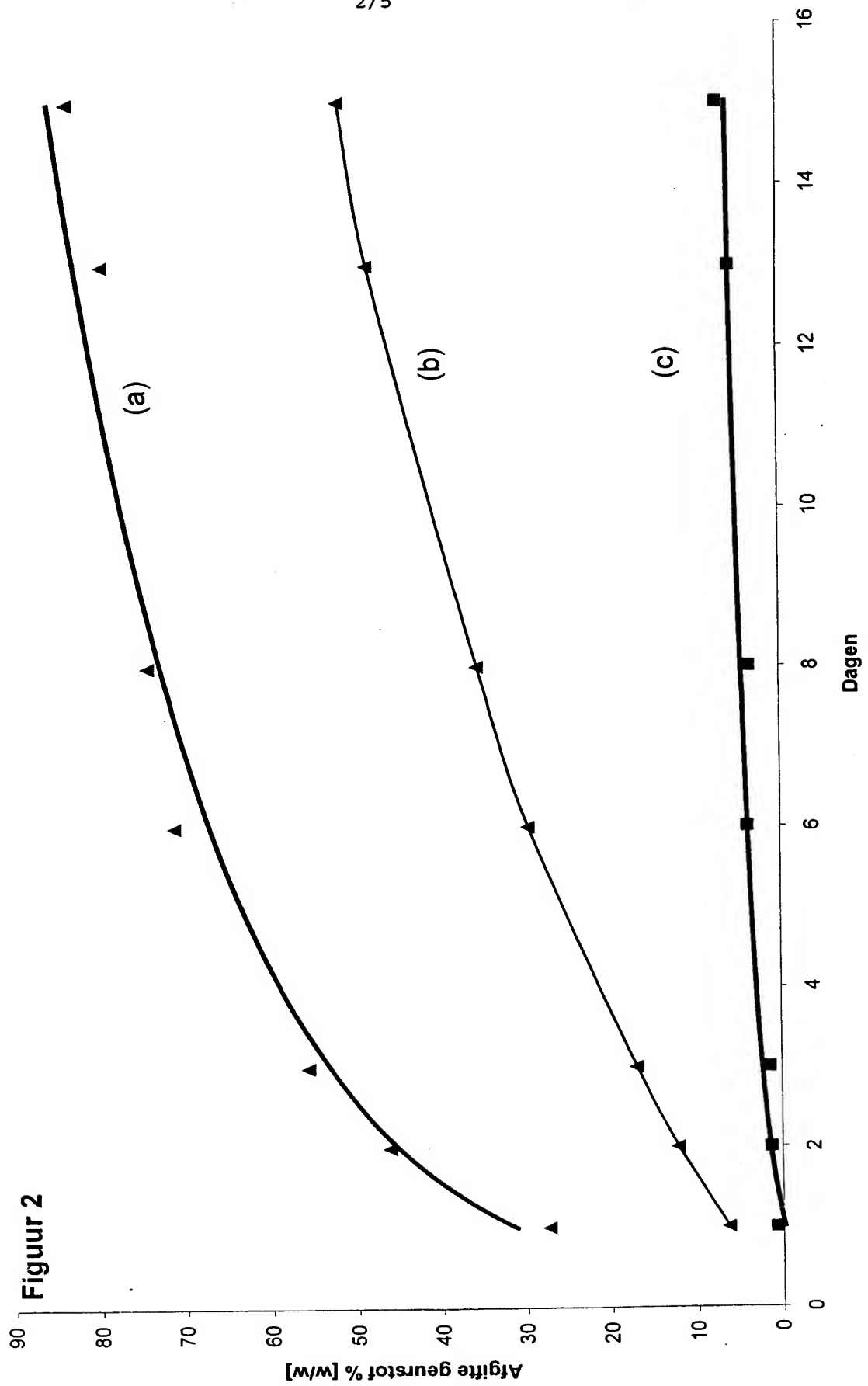
Dagen
(a)
(b)

Figuur 1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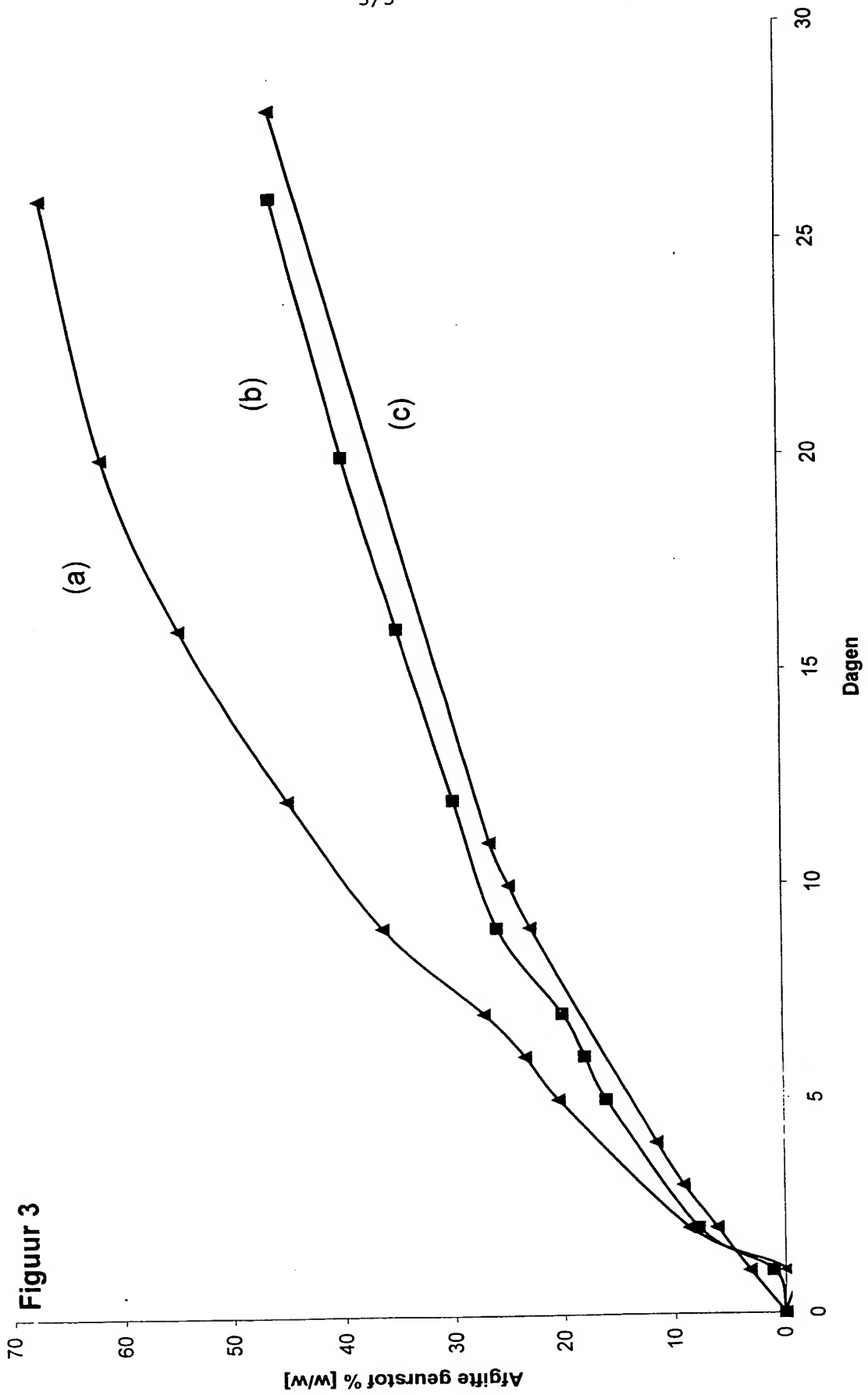
Dagen
(a)
(b)
(c)

Figuur 2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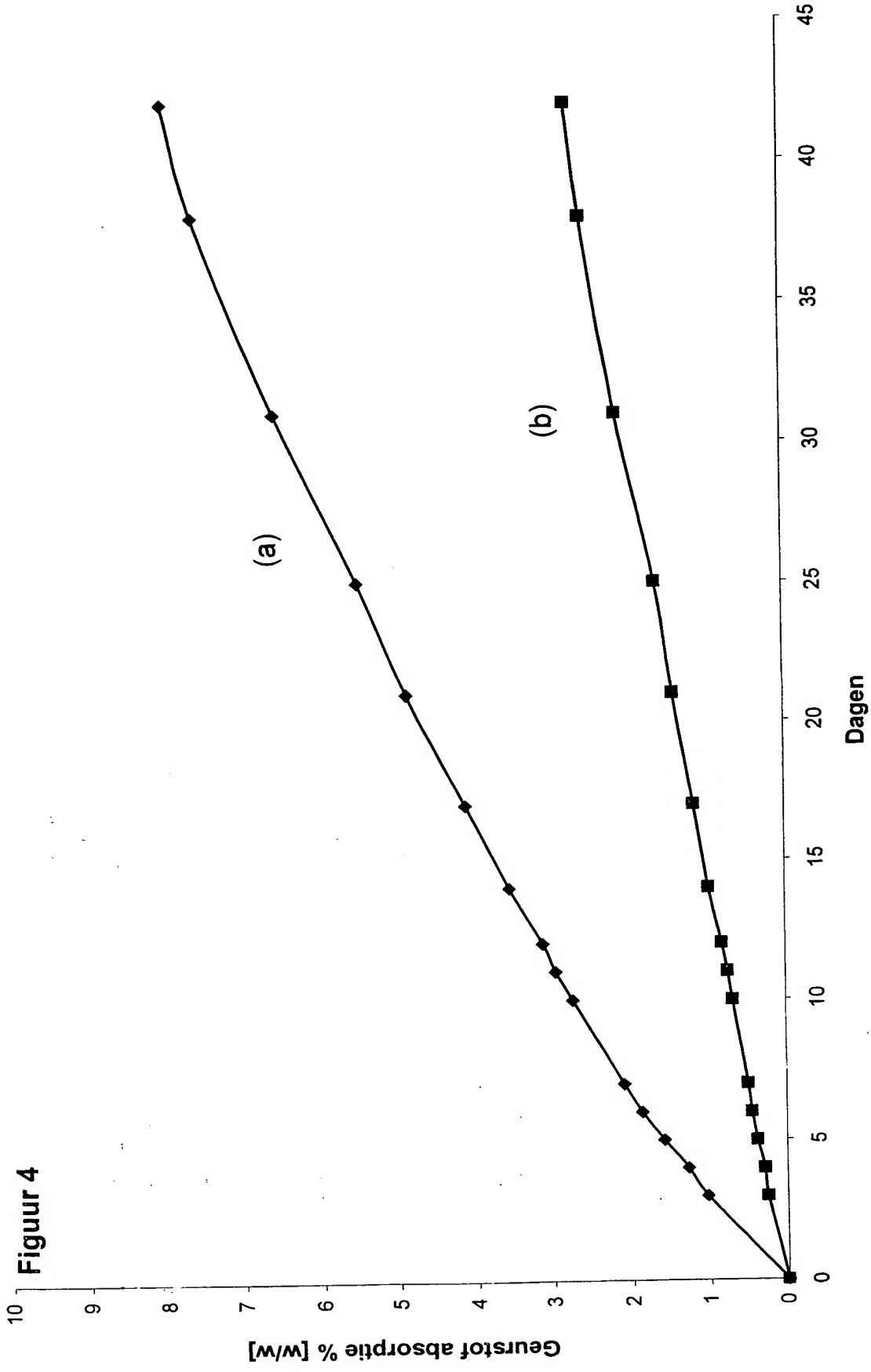
(b)
(c)

Figuur 3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(b)
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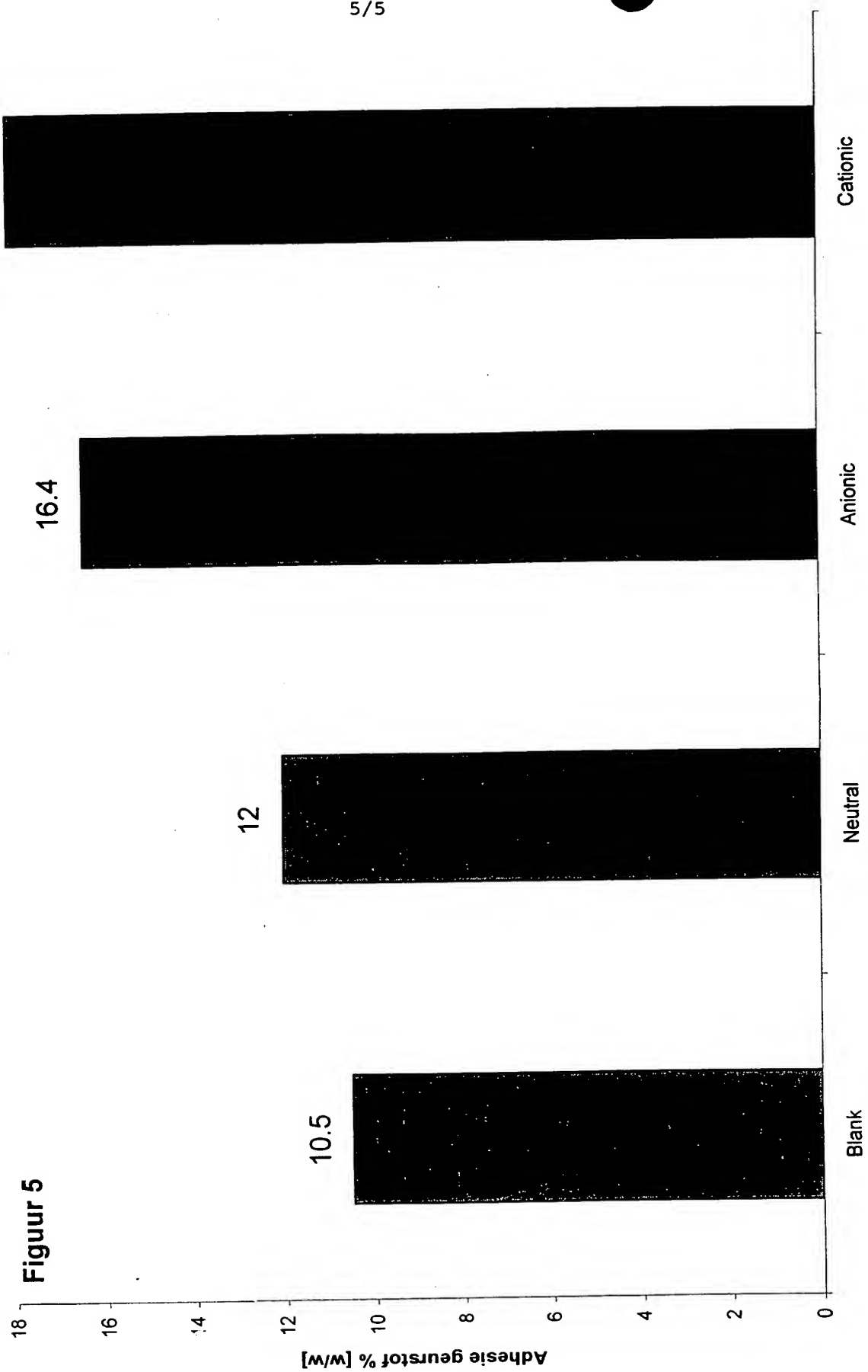
Figuur 4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16.4
18
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Neutral
Anionic
Cationic

Figuur 5

P49634PC00

Titel: Immobilisatie van actieve stoffen

De uitvinding heeft betrekking op een werkwijze voor het immobiliseren van actieve stoffen.

In de literatuur zijn verschillende methoden bekend voor het immobiliseren van actieve stoffen. Het doel van de immobilisatie is doorgaans het bereiken van een vertraagde en/of gecontroleerde afgifte van de actieve stof. Stoffen die gebruikt worden als dragermateriaal waarop de actieve stoffen zijn geïmmobiliseerd, zijn uiteenlopend van aard. Als voorbeeld zijn te noemen synthetische polymeren en biopolymeren zoals zetmeel of alginaten.

Uit de internationale octrooiaanvrage 89/03674 is een werkwijze bekend voor het bereiden van microbolletjes door een actieve stof, zoals paramagnetische deeltjes, in een zetmeeloplossing te suspenderen, het zetmeel met een fosfaat te verknopen en het zetmeel voor of na de verknoping in een hydrofoob medium te emulgeren.

Uit de Europese octrooiaanvrage 0 930 334 is een polysaccharide-conjugaat bekend, dat in staat is om cellulose te binden. Het conjugaat is gebaseerd op een polysaccharide, dat niet gemodificeerd is, en een deeltje dat een geurstof draagt. Het deeltje is bij voorkeur een poreus silicadeeltje, waarin de geurstof door diffusie kan binnendringen.

Het Amerikaanse octrooischrift 5,667,803 heeft betrekking op het gebruik van een zetmeelacetaat als hulpstof in farmaceutische gecompacteerde samenstellingen, voornamelijk tabletten. Afhankelijk van de substitutiegraad (DS) van het zetmeelacetaat, dient het te worden gebruikt als desintegreermiddel, vulmiddel, bindmiddel, of middel te regulering van de afgifte van een actieve stof uit een tablet. Er wordt niet gesproken over het immobiliseren van een actieve stof op het zetmeelacetaat. Het zetmeelacetaat

zelf kan in de toepassing van deze publicatie dan ook niet beschouwd worden als dragermateriaal.

In de internationale octrooiaanvrage 93/02712 is een werkwijze beschreven waarbij een olie-in-water emulsie van een oplosbare zetmeelfractie en een organisch oplosmiddel, zoals dichloormethaan, wordt bereid, waaraan een ontwateringsmiddel zoals een alcohol wordt toegevoegd. De aldus verkregen microbolletjes worden gefixeerd door retrogradatie van het zetmeel, dat daarom een hoog amylosegehalte dient te bezitten.

In de Nederlandse octrooiaanvrage 10.06444 is een verbetering op de bovengenoemde immobilisatiemethoden voorgesteld. Volgens de daarin beschreven werkwijze worden microdeeltjes, bestaande uit een werkzame stof in een zetmeelomhulling, bereid, door een olie-in-water emulsie van de werkzame stof in een hydrofobe fase en zetmeel in water te bereiden, deze emulsie op te nemen in een tweede hydrofobe fase, en het zetmeel vervolgens te verknopen. Eventueel kan de tweede hydrofobe fase uiteindelijk worden verwijderd. Een nadeel van deze werkwijze is dat bij verschillende typen werkzame stoffen is gevonden dat hoge beladingen van de werkzame stof in het microbolletje niet haalbaar zijn.

De Amerikaanse octrooischriften 3,455,838 en 5,354,559 en het Britse octrooischrift hebben alle betrekking op het inkapselen van actieve stoffen met water oplosbare of verkorte zetmelen, die eventueel gesubstitueerd zijn. De substitutiegraad (DS) van de beschreven zetmelen is telkens laag. De inkapseling vindt telkens plaats vanuit een emulsie of met behulp van een sproeidroogtechniek. Nadelig van de beschreven systemen is hun watergevoeligheid. Bij toepassing in een waterig milieu, bijvoorbeeld tijdens een wasproces, zullen de

kapsels gemakkelijk uiteenvallen waardoor de actieve stof op een ongewenst moment vrij komt in het water.

Verrassenderwijs is thans gevonden dat de hierboven genoemde nadelen kunnen worden verholpen door een specifiek dragermateriaal te gebruiken voor het immobiliseren van een actieve stof. Het specifieke dragermateriaal is een veresterd polysaccharide. De uitvinding betreft aldus een werkwijze voor het immobiliseren van een actieve stof, waarbij een mengsel wordt bereid van de actieve stof en een dragermateriaal in een vloeibare fase, waarna de vloeibare fase wordt omgezet in een vaste fase, waarbij het dragermateriaal een veresterd polysaccharide is.

Volgens de uitvinding worden zeer stabiele systemen verkregen. Hiermee wordt bedoeld dat bereikt wordt dat een actieve stof die volgens de uitvinding is geïmmobiliseerd in hoofdzaak niet onder ongewenste, en in hoofdzaak slechts onder gewenste, omstandigheden vrijkomt. Aldus kan volgens de uitvinding een bijzonder gunstig vertraagd afgifteprofiel ingesteld worden. Tevens wordt hiermee bedoeld dat door de immobilisatie de actieve stof beschermd wordt, zodat de kans op afbraak van de actieve stof door fysische of chemische invloeden aanzienlijk verminderd wordt. Aldus zal een volgens de uitvinding geïmmobiliseerde actieve stof een verlengde shelf-life hebben. Verder is het volgens de uitvinding mogelijk gebleken om een dragermateriaal met zeer grote hoeveelheden actieve stof te beladen.

Voorts is het een groot voordeel van de wijze van immobilisatie volgens de uitvinding dat deze zeer eenvoudig tot stand gebracht kan worden. Er behoeven vrijwel geen (ingewikkelde) handelingen te worden verricht voor het verkrijgen van het genoemde stabiele systeem.

Als gebruikt in deze tekst, verwijst de term "geïmmobiliseerde actieve stof" naar een complex van een actieve stof en een dragermateriaal.

Zoals gezegd, is het dragermateriaal dat volgens de uitvinding wordt gebruikt een veresterd polysaccharide. Voorbeelden van geschikte polysacchariden zijn zetmeel, cellulose, alginaten, pectine en combinaties daarvan. Bij voorkeur is het polysaccharide zetmeel of cellulose, bij bijzondere voorkeur zetmeel. Met veresterd zetmeel zijn zeer hoge beladingen te realiseren. Het zetmeel kan in beginsel van elke natuurlijke zetmeelbron afkomstig zijn. Geschikt is onder meer zetmeel afkomstig van aardappelen, maïs, tarwe, en tapioca. Bij voorkeur wordt granulair zetmeel gebruikt. Eventueel kan het zetmeel geheel of gedeeltelijk verstijfseld zijn.

Ter verkrijging van het gewenste veresterde polysaccharide kan uitgegaan worden van het natieve polysaccharide of van een derivaat daarvan. Geschikte derivaten in dit verband zijn bijvoorbeeld (gedeeltelijk) gehydrolyseerde polysacchariden, geoxideerde polysacchariden, geïoniseerde (zowel kationische als anionische) en veretherde polysacchariden. Overigens zal duidelijk zijn dat de reactie die wordt uitgevoerd uitgaande van natief polysaccharide ter verkrijging van één van de genoemde derivaten, tevens kan worden uitgevoerd met het reeds veresterde polysaccharide.

Het veresterde polysaccharide is bij voorkeur biodegradeerbaar. In de context van de uitvinding wordt onder een biodegradeerbaar materiaal een materiaal verstaan, dat de eigenschap heeft binnen een relatief korte tijd afgebroken te worden tot stoffen die bij voorkeur oplosbaar in water en niet toxisch zijn. De afbraak kan plaatsvinden door onder meer hydrolytische splitsing, onder

de invloed van licht, lucht, water en/of micro-organismen die in de natuur voorkomen.

De verestering zelf kan op elke bekende wijze worden uitgevoerd. Het polysaccharide kan bijvoorbeeld onderworpen worden aan een reactie met een zuuranhydride, dat de gewenste estergroep levert, in waterig, licht basisch milieu. Voorbeelden van geschikte veresteringsreacties zijn te vinden in R.L. Whistler, E.F. Paschall, Starch Chemistry and Technology", vol. 1 & 2 (1965), Academic Press Inc. De verestering wordt bij voorkeur zodanig uitgevoerd, dat een substitutiegraad (DS) wordt verkregen, waarbij het veresterde polysaccharide niet of slecht oplosbaar is in water. Gezien dit criterium hangt de gewenste substitutiegraad af van de aard van de estergroep. Wanneer de estergroep relatief apolair is, kan de waarde van de substitutiegraad liggen tussen 0,05 en een DS overeenkomend met een volledige substitutie, bij bijzondere voorkeur tussen 0,1 en 2,7. In het geval van een minder apolaire estergroep, zoals een acetaatgroep, is de substitutiegraad bij voorkeur iets hoger, te weten tussen 0,3 en 3, bij voorkeur tussen 0,3 en 2,7. Gevonden is dat de afgiftesnelheid van hydrofiele actieve stoffen groter is bij een relatief hoge DS, terwijl de afgiftesnelheid van hydrofobe actieve stoffen groter is bij een relatief lage DS.

Geschikte estergroepen die kunnen worden geïntroduceerd zijn onder meer acetaatgroepen, propionaatgroepen, butyraatgroepen, alkylsuccinaatgroepen waarbij de alkylgroep van 1-16 koolstofatomen bevat, benzoaatgroepen, en estergroepen die zijn afgeleid van carbonzuren met 1-18 koolstofatomen zoals verzadigde en één- of meervoudig onverzadigde vetzuren. Bij voorkeur wordt een acetaatester van een polysaccharide toegepast, omdat daarmee op bijzonder stabiele wijze een actieve stof geïmmobiliseerd kan worden.

De actieve stof die volgens de uitvinding wordt geïmmobiliseerd kan gekozen worden uit onder meer geneesmiddelen (bijvoorbeeld hormonen, ontstekingsremmers, insuline, chemotherapeutica, antibiotica, vaccins en dergelijke), bestijdingsmiddelen (zoals atachloor), paramagnetische stoffen, katalysatoren, organische reactanten, feromonen, lokstoffen, kosmetische actieve stoffen, wasactieve stoffen, desinfectanten, actieve stoffen voor textielbehandeling, actieve stoffen voor haarbehandeling, kleurstoffen, geurstoffen, smaakstoffen, en voedingsstoffen (bijvoorbeeld vitaminen, vetten, eiwitten, peptiden etc.) worden gebruikt. Natuurlijk kunnen er ook combinaties van de genoemde actieve stoffen worden geïmmobiliseerd. Bij voorkeur wordt een actieve stof gebruikt die oplosbaar of dispergeerbaar is in een hydrofobe fase.

In een voorkeursuitvoeringsvorm van de uitvinding is de actieve stof een geurstof. In het kader van de uitvinding wordt onder een geurstof een verbinding verstaan, die een bepaalde gewenste geur afgeeft. Tevens wordt onder een geurstof een mengsel van verbindingen verstaan, dat zodanig is samengesteld, dat de geuren van de verschillende componenten van het mengsel gezamenlijk een aangename of gewenste geur afgeven. Voorbeelden van verbindingen die individueel of gecombineerd gebruikt kunnen worden als geurstoffen zijn natuurlijke oliën, plantaardige en dierlijke extracten, synthetische oliën, alcoholen, aldehydes, ketonen, esters, lactonen, ethers, koolwaterstoffen, nitrillen en andere klassen van chemische verbindingen. Geurstoffen kunnen worden gebruikt om aan de omgeving of andere verbindingen of samenstellingen een gewijzigde, andere of versterkte geur te verlenen.

Door een geurstof volgens de uitvinding te immobiliseren wordt een zeer gunstig afgiftepatroon van de gewenste geur bewerkstelligd. Dankzij de hoge beladingen die haalbaar zijn, behoort bovendien een intenser of langer

afgiftepatroon dan voorheen tot de mogelijkheden. Bovendien is gebleken dat de shelf-life van geurstoffen sterk wordt verlengd door ze te immobiliseren volgens de uitvinding.

Teneinde de actieve stof te immobiliseren op het dragermateriaal, wordt in een vloeibare fase een homogeen mengsel gevormd van de actieve stof en het dragermateriaal. Dit kan op verschillende manieren worden gedaan.

Afhankelijk van de aard van het dragermateriaal en de actieve stof, kan door verwarmen van een mengsel van beide een vloeibare fase worden gevormd. In de vloeibare fase kan een zeer homogeen mengsel worden verkregen, bijvoorbeeld door roeren. Vervolgens kan door afkoelen een vaste fase worden gevormd, waarin de actieve stof is geïmmobiliseerd op het dragermateriaal.

Het is ook mogelijk om een oplossing of dispersie te vormen van het dragermateriaal en de actieve stof in een geschikt oplosmiddel, zodat de vloeibare fase wordt gevormd door het oplosmiddel. Door het oplosmiddel te verdampen kan de vaste fase worden verkregen, waarin de actieve stof is geïmmobiliseerd op het dragermateriaal. Geschikte oplosmiddelen kunnen afhankelijk van de aard van het dragermateriaal en de actieve stof worden verkregen. Bij voorkeur heeft het oplosmiddel een relatief laag kookpunt. Voorbeelden van oplosmiddelen die kunnen worden toegepast zijn aceton, diethylether, dichloormethaan, ethanol, methanol en isopropanol.

Het is overigens ook mogelijk om beide mogelijkheden te combineren en een smelt van het dragermateriaal en de actieve stof te bereiden in aanwezigheid van een kleine hoeveelheid van een oplosmiddel, zoals de hiervoor genoemde oplosmiddelen.

In een voorkeursuitvoering kunnen kleine deeltjes, zoals microbolletjes, geïmmobiliseerde actieve stof worden bereid door gebruik te maken van de op zich bekende

"solvent evaporation" methode. Hierbij wordt een emulsie bereid van de bovengenoemde vloeibare fase. De additionele vloeistof die daarbij nodig is, is bij voorkeur water, zodat een olie-in-water emulsie wordt verkregen. Desgewenst kan een geschikte emulgator, bijvoorbeeld polyethyleenglycol, worden gebruikt. Deze emulsie wordt vervolgens gedroogd, waarbij de beoogde deeltjes ontstaan. Deze kunnen worden geïsoleerd door bijvoorbeeld centrifuge.

Daarnaast is het mogelijk om gebruik te maken van de zogenaamde dubbele-emulsie technologie als beschreven in de Nederlandse octrooiaanvrage 10.06444. Hierin wordt een actieve stof ingekapseld door een olie-in-water emulsie van de actieve stof in een eerste hydrofobe fase en een oplossing of suspensie van het dragermateriaal in een waterige zetmeeldispersie of -oplossing te bereiden, welke olie-in-water emulsie vervolgens wordt opgenomen in een tweede hydrofobe fase. Wanneer deze technologie wordt toegepast in het kader van de onderhavige uitvinding, wordt de actieve stof samen met het dragermateriaal opgenomen in de eerste hydrofobe fase. Hierdoor is het mogelijk om de viscositeit van deze eerste hydrofobe fase in te stellen, hetgeen de inkapseling eenvoudiger maakt. Geschikte materialen voor gebruik als eerste en tweede hydrofobe fase kunnen door de vakman eenvoudig gevonden worden op basis van genoemde Nederlandse octrooiaanvrage in combinatie met zijn eigen vakkennis.

Volgens een andere uitvoeringsvorm wordt een gasvormige actieve geïmmobiliseerd op het bovenbeschreven dragermateriaal. Teneinde dit te bereiken kan het dragermateriaal in een vloeibare fase worden toegepast, deze fase kan worden verkregen door het dragermateriaal te verwarmen of door het op te lossen of te dispergeren in een geschikt oplosmiddel. Indien gewenst, kan na immobilisatie van de gasvormige actieve stof de vloeibare fase worden

omgezet in een vaste fase door afkoelen of verwijderen van het oplosmiddel. Het is tevens mogelijk om de gasvormige actieve stof te immobiliseren door deze in contact te brengen met het dragermateriaal in vaste vorm.

Het is volgens de uitvinding mogelijk gebleken om actieve stoffen, met name geurstoffen, te absorberen. Gevonden is dat het onderhavige dragermateriaal zeer geschikt is om geurstoffen in te vangen. Aldus kan bijvoorbeeld textiel dat onaangenaam ruikt worden behandeld met het dragermateriaal, als hierboven omschreven, waardoor de geurstof die de ongewenste geur verspreidt, wordt geïmmobiliseerd op het dragermateriaal. Hiermee wordt bereikt dat de geur minder wordt, althans minder waarneembaar wordt. De geurstof die ingevangen wordt, kan in de vaste, vloeibare of gasvormige fase verkeren. Wanneer de geurstof in de gasvorm verkeert, is gevonden dat deze kan worden ingevangen door het dragermateriaal in vaste vorm. Daarnaast kan het dragermateriaal in een vloeibare fase worden gebruikt om de geurstof te absorberen. Na eventueel drogen of afkoelen kan de vaste, geïmmobiliseerde actieve stof eenvoudig worden verwijderd. Aldus heeft de uitvinding tevens betrekking op de toepassing van een veresterd polysaccharide voor het fixeren of immobiliseren van een actieve stof, waarbij de actieve stof bij voorkeur een geurstof is.

Deze uitvoeringsvorm van de uitvinding kan geschikt worden toegepast voor het wegnemen van tal van onaangename geuren, bijvoorbeeld veroorzaakt door lichaamsvocht, (oksel)deodoranten, persoonlijke hygiëneproducten, zoals (incontinentie)luiers, damesverband, inlegkruisjes, tissues, (papieren) servetten of handdoeken, en toiletpapier, luchtverfrissers, ruimtedeodoranten, vullingen voor kattenbakken. In een voorkeursuitvoeringsvorm kan een product, zoals

(incontinentie)luiers, damesverband, inlegkruisjes, tissues, papieren servetten of handdoeken, toiletpapier of vulling voor kattenbakken worden voorzien van het dragermateriaal volgens de uitvinding, zodat deze in gebruik minder onaangename geuren verspreiden.

De beladingsgraad die volgens de uitvinding kan worden bereikt hangt mede af van de aard van het dragermateriaal, de actieve stof en de toepassing. Meestal zal de belading liggen tussen 0,1 en 99 gew.%, in het bijzonder tussen 1 en 50 gew.%, betrokken op het totale gewicht aan droge stof van het dragermateriaal.

Desgewenst kan de vaste, geïmmobiliseerde actieve stof, al dan niet gemodificeerd als hierboven beschreven, worden verwerkt tot een poeder, bijvoorbeeld door te malen. De deeltjesgrootte van het poeder kan worden gekozen afhankelijk van de beoogde toepassing van de geïmmobiliseerde actieve stof. Het is ook mogelijk om de geïmmobiliseerde actieve stof in grotere vormen toe te passen. Dergelijke vormen kunnen worden verkregen door toepassing van gebruikelijke polymeervormgevingstechnieken zoals extruderen, waaronder film- en folie-extruderen, spuitgieten, persen of vacuümtrekken.

Teneinde de verwerkbaarheid en toepasbaarheid van de geïmmobiliseerde actieve stof te beïnvloeden, kan een chemische of fysische modificatie aan het oppervlak van het dragermateriaal worden uitgevoerd. Voorbeelden van geschikte modificaties zijn gedeeltelijke hydrolyse van het dragermateriaal, verknoping van het dragermateriaal en ionisatie van het dragermateriaal, en combinaties daarvan. Het zal de vakman duidelijk zijn dat allerlei op zich bekende modificaties onder omstandigheden in aanmerking komen. Bij voorkeur wordt slechts een deel van het dragermateriaal, bij voorkeur minder dan 5 gew.%, nog

liever minder dan 1 gew.%, van de totale hoeveelheid dragermateriaal, gemodificeerd.

Gedeeltelijke hydrolyse van het dragermateriaal leidt ertoe dat de geïmmobiliseerde actieve stof een meer hydrofiel karakter verkrijgt, hetgeen gewenst kan zijn wanneer toepassingen in waterig milieu beoogd worden. De hydrolyse kan worden uitgevoerd door bij voorbeeld deeltjes, van het dragermateriaal te suspenderen in water. Eventueel kan een kleine hoeveelheid (0,1-2 gew.%, betrokken op het gewicht van de deeltjes) surfactant, zoals natriumdodecylsulfaat of een alkyl(poly)glucoside worden toegevoegd. Desgewenst kan de hydrolyse worden versneld door de pH van de suspensie te veranderen of de temperatuur te verhogen. Bij voorkeur wordt gewerkt bij een pH tussen 8 en 13 en een temperatuur tussen 20 en 40°C.

Verknoping van het oppervlak van de deeltjes kan worden uitgevoerd om de geïmmobiliseerde actieve stof minder oplosbaar in water te maken. Dit kan gewenst zijn nadat een gedeeltelijke hydrolyse of andere modificatie is uitgevoerd. Wanneer verknoping in combinatie met een gedeeltelijke hydrolyse wordt toegepast, wordt een geïmmobiliseerde actieve stof verkregen die niet oplost in water, maar daarin wel zeer goed te verwerken is, bijvoorbeeld in de vorm van een suspensie. Daarnaast leidt verknoping ertoe dat de actieve stof bijzonder goed wordt vastgehouden door het dragermateriaal. De verknoping kan worden uitgevoerd door een reactie met een geschikt verknopingsmiddel, zoals trinatriumfosfaat of epichloorhydrine. Hiertoe wordt bijvoorbeeld een suspensie bereid van de deeltjes in water, eventueel in aanwezigheid van een kleine hoeveelheid (0,1-2 gew.%, betrokken op het gewicht van de deeltjes) surfactant, zoals natrium-dodecylsulfaat of een alkyl(poly)glucoside, waaraan het verknopingsmiddel wordt toegevoegd in een hoeveelheid van

0,5-3 gew.%, betrokken op het gewicht van de deeltjes. Bij voorkeur wordt een kleine hoeveelheid (0,5-5 gew.%, betrokken op het gewicht van de deeltjes) van een base, bijvoorbeeld NaOH of KOH, toegevoegd. Andere voorbeelden van mogelijke verknopingsreacties zijn beschreven in R.L. Whistler, E.F. Paschall, "Starch Chemistry and Technology", vol. 1 & 2 (1965), Academic Press Inc.

Door het aanbrengen van positief of negatief geladen groepen kan de interactie van de geïmmobiliseerde actieve stof met de omgeving worden ingesteld. Zo kan bijvoorbeeld worden bereikt dat de geïmmobiliseerde actieve stof goed hecht aan andere materialen, zoals textiel. Daarnaast kan de dispergeerbaarheid van de geïmmobiliseerde actieve stof positief worden benvloed. Het aanbrengen van positief of negatief geladen groepen aan het oppervlak kan in beginsel worden uitgevoerd op elke bekende manier om geladen groepen te introduceren in een polysaccharidemateriaal. Voorbeelden van geschikte methoden zijn onder meer beschreven in R.L. Whistler, E.F. Paschall, "Starch Chemistry and Technology", vol. 1 & 2 (1965), Academic Press Inc. Quaternaire ammoniumgroepen en carboxyl- of fosfaatgroepen hebben de voorkeur.

De actieve stof kan worden afgegeven aan een doelomgeving door chemische, fysische of enzymatische invloeden. Deze invloeden zullen doorgaans het dragermateriaal (gedeeltelijk) afbreken of zodanig modificeren dat de actieve stof vrijkomt. De actieve stof kan bijvoorbeeld in het spijsverteringskanaal worden afgegeven onder invloed van de heersende omstandigheden in de diverse organen (pH, enzymen). Eventueel kan de gevoeligheid van dragermateriaal worden aangepast door uit te gaan van een ander veresterd polysaccharidederivaat. In wasmiddelen kan de afgifte worden bevorderd door temperatuurverhoging of ook weer door pH- of

enzyminvloeden. Op of in cultuurgrond of potgrond kan de afgifte worden bewerkstelligd door hydrolyse of inwerking van zouten. In reactiemengsels kan de afgifte ook worden bewerkstelligd door invloed van bijvoorbeeld elektrische stroom of pH-verandering.

De geïmmobiliseerde actieve stof kan worden gebruikt in uiteenlopende toepassingen. Voorbeelden omvatten wasmiddelen, wasverzachters, schoonmaakmiddelen (zoals reinigers, detergenten, desinfectanten, afwasmiddelen, vaatwasmiddelen, spoelmiddelen, bleekmiddelen, en toiletreinigers), textielbehandelingsmiddelen, textielsprays, strijkhulpmiddelen, wasdrogertoevoegingen, optische witmakers, geurmaskeringsmiddelen, persoonlijke hygiëneproducten, meststoffen, voedingsmiddelen, smaakstoffen, farmaceutische middelen, tissues, cosmetica (zoals parfums, eau de colognes, bad- en doucheproducten, shampoos, haarverzorgingsmiddelen, huidverzorgingsmiddelen, zonnebrandmiddelen, crèmes, lotions, aerosols, en zepen), bodemverbeteraars, bestrijdingsmiddelen (tegen schimmels, bacteriën, insekten, mijten, aaltjes en dergelijke), bekledingslagen of coatings, verven, inkten, organische reactanten (waterstofperoxide), katalyse, en diagnostica.

De uitvinding zal thans nader worden toegelicht aan de hand van de volgende voorbeelden.

Voorbeeld 1 (Immobilisatie van een geurstof op een dragermateriaal)

A. Paselli-acetaat (10 g) wordt opgelost in een mengsel van geurstof (5 g) en aceton (5 g), eventueel onder verwarming (50°C). Vervolgens wordt het vluchtige oplosmiddel aceton verwijderd door het materiaal te verwarmen bij 80°C. Na afkoelen wordt een hard bros materiaal met een geurstofbelading van ongeveer 33

gewicht% verkregen. Het materiaal wordt, eventueel cryogeen, gemalen tot een poeder.

B. Paselli-acetaat (10 g) wordt opgelost in een mengsel van geurstof (5 g) en aceton (5 g), eventueel onder verwarming (50°C). Vervolgens wordt een dunne film gevormd van Paselli-acetaat/geurstof door de oplossing uit te gieten op glas en het vluchtige oplosmiddel aceton te laten verdampen.

C. Paselli-acetaat (10 g) wordt opgelost of gesuspendeerd in geurstof (5 g) en in een afgesloten reactor bij 105°C verwarmd gedurende 2 uur. Na afkoelen wordt een hard bros materiaal met een geurstofbelading van ongeveer 33% verkregen. Het materiaal wordt, eventueel cryogeen, gemalen tot een poeder.

D. Paselli acetaat poeder (500 mg) wordt in een verzadigde atmosfeer van geurstof gebracht. Afhankelijk van de absorptietijd en de temperatuur kan de belading ingesteld worden, zie ook figuur 4. Het materiaal wordt, eventueel cryogeen, gemalen tot een poeder.

E. Cellulose-acetaat (10 g) wordt opgelost in een mengsel van geurstof (5 g) en aceton (5 g), eventueel onder verwarming (50°C). Vervolgens wordt het vluchtige oplosmiddel aceton verwijderd door het materiaal te verwarmen bij 80°C. Na afkoelen wordt een hard bros materiaal met een geurstofbelading van ongeveer 33 gewicht% verkregen. Het materiaal wordt, eventueel cryogeen, gemalen tot een poeder.

Voorbeeld 2 (chemische modificaties aan oppervlak van de geïmmobiliseerde actieve stof)

A. Een combinatie van hydrolyse en verknoping wordt uitgevoerd in water. Paselli-acetaat/geurstof poeder (10 g) wordt gesuspendeerd in 50 g water met 20 mg SDS (natriumdodecylsulfaat). Vervolgens wordt er 0.2-0.4 g NaOH toegevoegd en 0.1 g epichloorhydrine. De suspensie wordt gedurende 18 uur geroerd bij kamertemperatuur. Het materiaal wordt vervolgens gewassen en gescheiden d.m.v. centrifugeren.

B. Anionisering: Paselli-acetaat/geurstof poeder (10 g) wordt gesuspendeerd in 50 g water met 20 mg SDS (natriumdodecylsulfaat). Een oplossing van 0.1 g NaOH in 1 ml water wordt toegevoegd en vervolgens wordt 18 uur geroerd. Vervolgens wordt er NaBr (0.1 g), Tempo (20 mg, 2,2,6,6-tetramethylpiperidine-1-oxide) en natriumhypochloriet oplossing (10g; 4g Cl+/100g) toegevoegd. De pH van de reactie wordt gedurende 30 minuten op 10 gehouden. Het materiaal wordt gewassen en gescheiden d.m.v. centrifugeren.

C. Anionisering: Paselli-acetaat/geurstof poeder (15 g) wordt gesuspendeerd in 250 g water met 20 mg SDS (natriumdodecylsulfaat). Vervolgens wordt er TSTP (trinatriumtrifosfaat; 2.0 g) toegevoegd terwijl de pH op 12 wordt gehouden gedurende 1-2 uur. Het materiaal wordt gewassen en gescheiden d.m.v. centrifugeren.

D. Kationisering: Paselli-acetaat/geurstof poeder (5 g) wordt gesuspendeerd in 50 g water met 10 mg SDS (natriumdodecylsulfaat). Vervolgens wordt er glycidyltrimethyl-ammoniumchloride (GMAC; 0.2 g), epichloorhydrine (0.05 g) en een oplossing van 0.25 g NaOH in 1 g water toegevoegd. De suspensie wordt

gedurende 18 uur geroerd bij kamertemperatuur. Het materiaal wordt gewassen en gescheiden d.m.v. centrifugeren.

Voorbeeld 3 (afgiftegedrag van geurstoffen)

A. Figuur 1 geeft de afgifteprofielen weer van een wel- (a) en niet- (b) geïmmobiliseerd geurstofmengsel (ACB 56SE) aangebracht op textiel. De figuur laat duidelijk verschillend afgiftegedrag zien. Het geurstofmengsel is geïmmobiliseerd op een dragermateriaal bestaande uit Paselli-acetaat met een DS van 3.

B. Figuur 2 geeft de afgifteprofielen van drie geïmmobiliseerde geurstoffen, nl. Linalool (a), Tilianol Super (b) en Hydroxycitronellal (c). De figuur laat duidelijk zien dat de geurstoffen een van elkaar verschillend afgiftegedrag vertonen. De geurstoffen zijn geïmmobiliseerd op een dragermateriaal bestaande uit Paselli-acetaat met een DS van 3.

C. Figuur 3 geeft de afgifteprofielen van Jasmacyclene, geïmmobiliseerd op verschillende dragermaterialen bestaande uit Paselli-acetaat met een DS van 1.0 (a), 1.7 (b) en 3 (c). De figuur laat duidelijk zien dat de actieve stof een lagere afgiftesnelheid vertoont bij een hogere substitutiegraad.

Voorbeeld 4 (absorptiegedrag van dragermateriaal)

Figuur 4 geeft het absorptiegedrag bij kamertemperatuur voor de geurstof Frutalone op een poedervormig Paselli-acetaat dragermateriaal met een DS van 3. De hoeveelheid dragermateriaal (0.1 gram (a) of 0.5 gram (b)) die aanwezig is in de verzadigde geurstofdamp is van invloed op de absorptiesnelheid.

Voorbeeld 5 (hechting van geïmmobiliseerde geurstof aan textiel tijdens wassen)

Paselli-acetaat/Tonalid poeder (DS = 3; belading = 33%) wordt in water gesuspendeerd in aanwezigheid van textiel (katoen). Gewassen wordt bij pH 10.4; T = 60°C gedurende 1 uur. Vervolgens wordt het textiel gespoeld met water en gedroogd. De op het textiel aanwezige geurstof wordt geëxtraheerd m.b.v. dichloorethaan en geanalyseerd met behulp van gaschromatografie. Figuur 5 geeft de adhesie, d.w.z. het percentage van de totale geurstof die is gehecht aan het textiel tijdens het wassen, voor enkele verschillende modificaties en een blanco experiment met normaal, d.w.z. niet geïmmobiliseerd, Tonalid. De figuur laat zien dat de hechting van de geurstof toeneemt door de beschreven immobilisatie en modificaties.
In figuur 5 wordt getoond van links naar rechts: *blank* (= blanco, d.w.z. niet geïmmobiliseerd Tonalid); *neutral* (= geïmmobiliseerd Tonalid); *anionic* (= geïmmobiliseerd Tonalid, met geanioniseerd oppervlak); *cationic* (= geïmmobiliseerd Tonalid, met gekationiseerd oppervlak).

Voorbeeld 6 (solvent evaporation methode)

2 gram geacetyleerd zetmeel (DS = 3) werd samen met 1 gram van de geurstof frutalone opgelost in 10 ml dichloormethaan, analoog aan de procedure van voorbeeld 1. Het verkregen mengsel werd geëmulgeerd in 200 ml water onder toepassing van 3 gew.% polyethyleenglycol (Mw = 1000) als emulgator. Hierbij werd een ultrasone sonde gebruikt (50 output; 2 min.). Solvent evaporation werd vervolgens uitgevoerd bij roeren (top-stirrer; 500 rpm) gedurende 2 uur bij kamertemperatuur en omgevingsdruk. De aldus

verkregen microbolletjes werden verzameld door centrifugeren (27.000 g; 15 min.). Vervolgens werden de deeltjes gedroogd aan de lucht bij kamertemperatuur en een luchtvochtigheid van 30% RH. De belading bleek na meting met GC 28 gew.% te zijn.

CONCLUSIES

1. Werkwijze voor het immobiliseren van een actieve stof, waarbij een mengsel wordt bereid van de actieve stof en een dragermateriaal in een vloeibare fase, waarna de vloeibare fase wordt omgezet in een vaste fase, waarbij het dragermateriaal een veresterd polysaccharide is.

2. Werkwijze volgens conclusie 1, waarbij de vloeibare fase wordt verkregen door de actieve stof en het dragermateriaal te mengen en te verwarmen tot een homogeen, vloeibaar mengsel wordt verkregen, en waarbij de vaste fase wordt verkregen door afkoelen.

3. Werkwijze volgens conclusie 1, waarbij de vloeibare fase wordt verkregen door de actieve stof en het dragermateriaal op te lossen of te dispergeren in een oplosmiddel, en waarbij de vaste-fase wordt verkregen door het oplosmiddel te verdampen.

4. Werkwijze volgens conclusie 3, waarbij het oplosmiddel is gekozen uit de groep van aceton, dichloormethaan, diethylether, ethanol, methanol en iso-propanol.

5. Werkwijze volgens conclusies 1-4, waarbij de vloeibare fase wordt geëmulgeerd in een vloeistof en waarbij kleine deeltjes worden gevormd van de geïmmobiliseerde actieve stof door de vloeistof te verdampen.

6. Werkwijze volgens conclusie 5, waarbij de vloeistof water is.

7. Werkwijze volgens conclusie 1, waarbij de vloeibare fase een dubbele emulsie is, welke wordt gevormd door een olie-in-water emulsie te bereiden van de actieve stof in een eerste hydrofobe fase en een oplossing of suspensie van het dragermateriaal in een waterige zetmeeloplossing of -dispersie en deze olie-in-water emulsie op te nemen in een tweede hydrofobe fase en waarbij de vaste fase wordt

gevormd door het zetmeel te verknopen en de tweede hydrofobe fase te verwijderen.

8. Werkwijze voor het immobiliseren van een actieve stof, waarbij de actieve stof in gasvorm in contact wordt gebracht met een dragermateriaal in vaste fase of een vloeibare fase, waarbij het dragermateriaal een veresterd polysaccharide is.

9. Werkwijze volgens een van de voorgaande conclusies, waarbij het veresterde polysaccharide een veresterd zetmeel, cellulose, alginaat, pectine, of een derivaat daarvan is.

8. 10. Werkwijze volgens een van de voorgaande conclusies, waarbij het polysaccharide is veresterd met een acetaatgroep, een propionaatgroep, een butyraatgroep, een alkylsuccinaatgroep, waarbij de alkylgroep van 1-16 koolstofatomen bevat, een benzoaatgroep, of een estergroep die is afgeleid van een carbonzuur met 1-18 koolstofatomen.

11. Werkwijze volgens een van de voorgaande conclusies, waarbij het polysaccharide een substitutiegraad (DS) heeft tussen 0,05 en een DS overeenkomend met nagenoeg volledige substitutie.

12. Werkwijze volgens één van de voorgaande conclusies, waarbij de actieve stof is gekozen uit de groep van geneesmiddelen, bestrijdingsmiddelen, paramagnetische stoffen, katalysatoren, organische reactanten, kosmetische actieve stoffen, kleurstoffen, geurstoffen, smaakstoffen en voedingsstoffen.

13. Werkwijze volgens één van de voorgaande conclusies, waarbij de geïmmobiliseerde actieve stof tot een poeder wordt gevormd.

14. Werkwijze volgens één van de voorgaande conclusies, waarbij de geïmmobiliseerde actieve stof wordt verwerkt door toepassing van polymeervormgevingstechnieken, zoals extruderen, spuitgieten, persen of vacuümtrekken.

15. Werkwijze volgens één van de voorgaande conclusies, waarbij aan het oppervlak van de geïmmobiliseerde actieve stof een fysische of chemische modificatie wordt uitgevoerd.

16. Geïmmobiliseerde actieve stof verkrijgbaar door een werkwijze volgens één van de voorgaande conclusies.

17. Toepassing van een geïmmobiliseerde actieve stof volgens conclusie 16 in een wasmiddel, wasverzachter, schoonmaakmiddel, zeep, shampoo, textielbehandelingsmiddel, textielspray, strijkhulpmiddel, wasdrogertoevoeging, optische witmaker, geurmaskeringsmiddel, persoonlijke hygiëneproduct, meststof, voedingsmiddel, smaakstof, farmaceutisch middel, tissue, cosmetica, bodemverbeteraars, bestrijdingsmiddel, bekledingslaag of coating, verf, inkt, in de organische synthese, de diagnostica of de landbouw.

18. Toepassing van een veresterd polysaccharide voor het fixeren of immobiliseren van een actieve stof.

17. 19. Toepassing volgens conclusie 18, waarbij de actieve stof een geurstof is.

20. Toepassing volgens conclusie 19 voor het verminderen van een geur.

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UITTREKSEL

De uitvinding heeft betrekking op een werkwijze voor het immobiliseren van een actieve stof, waarbij een mengsel wordt bereid van de actieve stof en een dragermateriaal in een vloeibare fase, waarna de vloeibare fase wordt omgezet in een vaste fase, waarbij het dragermateriaal een veresterd polysaccharide is. De uitvinding betreft voorts de toepassing van een versterd polysaccharide voor het fixeren of immobiliseren van actieve stoffen, met name van geurstoffen.

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(54) Title: IMMOBILIZATION OF ACTIVE SUBSTANCES

(57) Abstract: The invention relates to a method for immobilizing an active substance, wherein a mixture is prepared of the active substance and a carrier material in a liquid phase, whereafter the liquid phase is converted to a solid phase, the carrier material being an esterified polysaccharide. The invention further relates to the use of an esterified polysaccharide for fixing or immobilizing active substances, in particular odorous substances.

Titl : Immobilization of active substances

This invention relates to a method for immobilizing active substances.

In the literature, different methods are known for the immobilization of active substances. The purpose of the immobilization is normally to achieve a slowed and/or controlled release of the active substance. Substances that are used as carrier material on which the active substances are immobilized vary in nature. To be mentioned by way of example are synthetic polymers and biopolymers such as starch or alginates.

International patent application 89/03674 discloses a method for preparing microspheres by suspending an active substance, such as paramagnetic particles, in a starch solution, crosslinking the starch with a phosphate, and emulsifying the starch in a hydrophobic medium before or after crosslinking.

European patent application 0 930 334 discloses a polysaccharide conjugate which is capable of binding cellulose. The conjugate is based on a polysaccharide, which is not modified, and a particle that carries a perfume. The particle is preferably a porous silica particle, into which the perfume can penetrate through diffusion.

U.S. Patent 5,667,803 relates to the use of a starch acetate as auxiliary substance in pharmaceutical compacted compositions, mainly tablets. Depending on the degree of substitution (DS) of the starch acetate, it is to be used as disintegrator, filler, binder, or agent for regulating the release of an active substance from a tablet. No mention is made of the immobilization of an active substance on a starch acetate. Accordingly, the starch acetate itself cannot, in the application of this publication, be regarded as carrier material.

International patent application 93/02712 discloses a method in which an oil-in-water emulsion of a soluble starch fraction and an organic

solvent, such as dichloromethane, is prepared, to which a dehydrating agent such as an alcohol is added. The thus obtained microspheres are fixed by retrogradation of the starch, which must therefore have a high amylose content.

Dutch patent application 10.06444 proposes an improvement of the above-mentioned immobilization methods. According to the method described therein, microparticles consisting of an effective substance in a starch envelope are prepared by preparing an oil-in-water emulsion of the effective substance in a hydrophobic phase and starch in water, including this emulsion in a second hydrophobic phase, and subsequently crosslinking the starch. Optionally, the second hydrophobic phase can eventually be removed. A disadvantage of this method is that with different types of effective substances it has been found that high degrees of loading of the effective substance in the microsphere are not feasible.

U.S. Patents 3,455,838 and 5,354,559 and the British Patent Specification all relate to the encapsulation of active substances with water-soluble or shortened starches, which are optionally substituted. The degree of substitution (DS) of the starches described is low in each case. The encapsulation in each case takes place from an emulsion or with the aid of a spray-drying technique. A disadvantage of the systems described is their water-sensitivity. When used in an aqueous medium, for instance during a washing process, the capsules will easily disintegrate, so that the active substance is released into the water at an undesired time.

Surprisingly, it has presently been found that the above-mentioned disadvantages can be obviated by using a specific carrier material for the immobilization of an active substance. The specific carrier material is an esterified polysaccharide. The invention thus relates to a method for immobilizing an active substance, wherein a mixture is prepared of the active substance and a carrier material in a liquid phase, whereafter the

liquid phase is converted to a solid phase, the carrier material being an esterified polysaccharide.

According to the invention, highly stable systems are obtained This is understood to mean that it is accomplished that an active substance which is immobilized according to the invention is substantially not released under undesired conditions and is substantially released only under desired conditions. Thus, according to the invention, a particularly favorable slowed-release profile can be set. This is also understood to mean that through the immobilization the active substance is protected, so that the chance of breakdown of the active substance through physical or chemical influences is reduced considerably. Thus, an active substance immobilized according to the invention will have a prolonged shelf life. Further, according to the invention, it has been found possible to load a carrier material with very large amounts of active substance.

Further, it is a great advantage of the manner of immobilization according to the invention that it can be effected very simply. Virtually no (complex) operations need to be performed to obtain the stable system referred to.

As used in this text, the term "immobilized active substance" refers to a complex of an active substance and a carrier material.

As said, the carrier material that is used according to the invention is an esterified polysaccharide. Examples of suitable polysaccharides are starch, cellulose, alginates, pectin and combinations thereof. Preferably, the polysaccharide is starch or cellulose, starch being particularly preferred. With esterified starch, very high loading degrees are feasible. In principle, the starch can originate from any natural starch source. Suitable, among others, is starch coming from potatoes, corn, wheat, and tapioca. Preferably, granular starch is used. Optionally, the starch can be wholly or partly gelatinized.

To obtain the desired esterified polysaccharide, it is possible to start from the native polysaccharide or from a derivative thereof. Suitable derivatives in this connection are, for instance, (partially) hydrolyzed polysaccharides, oxidized polysaccharides, ionized (both cationic and anionic) and etherified polysaccharides. Incidentally, it will be clear that the reaction that is performed starting from native polysaccharide to obtain any one of the derivatives mentioned can also be performed with the polysaccharide already esterified.

The esterified polysaccharide is preferably biodegradable. In the context of the invention, a biodegradable material is understood to mean a material that has the property of being broken down within a relatively short time into substances that are preferably soluble in water and non-toxic. The breakdown can take place *inter alia* through hydrolytic cleavage, under the influence of light, air, water and/or microorganisms occurring in nature.

The esterification proper can be carried out in any known manner. The polysaccharide can, for instance, be subjected to a reaction with an acid anhydride, which provides the desired ester group, in aqueous, slightly alkaline medium. Examples of suitable esterification reactions are to be found in R.L. Whistler, E.F. Paschall, "Starch Chemistry and Technology", vol. 1 & 2 (1965), Academic Press Inc. The esterification is preferably carried out so as to yield a degree of substitution (DS) at which the esterified polysaccharide is not soluble or poorly soluble in water. In view of this criterion, the desired degree of substitution depends on the nature of the ester group. When the ester group is relatively non-polar, the value of the degree of substitution can be between 0.05 and a DS corresponding to a complete substitution, and preferably, in particular, between 0.1 and 2.7. In the case of a less non-polar ester group, such as an acetate group, the degree of substitution is preferably slightly higher, viz. between 0.3 and 3, preferably between 0.3 and 2.7. It has been found that the release rate of

hydrophilic active substances is higher at a relatively high DS, while the release rate of hydrophobic active substances is higher at a relatively low DS.

Suitable ester groups that can be introduced are *inter alia* acetate groups, propionate groups, butyrate groups, alkyl succinate groups, in which the alkyl group contains from 1 to 16 carbon atoms, benzoate groups, and ester groups which are derived from carboxylic acids having from 1 ~~to~~ 18 carbon atoms, such as saturated and monounsaturated or polyunsaturated fatty acids. Preferably, an acetate ester of a polysaccharide is used, because an active substance can be immobilized with it in a particularly stable manner.

The active substance which is immobilized according to the invention can be selected from *inter alia* medicines (for instance hormones, antiinflammatory agents, insulin, chemotherapeuticals, antibiotics, vaccines and the like), plant protection agents (such as atachloride), paramagnetic substances, catalysts, organic reactants, pheromones, lures, cosmetic actives, washing active substances, disinfectants, fabric conditioning actives, hair conditioning actives, colorants, fragrance, flavor, and nutrients (for instance vitamins, fats, proteins, peptides, etc.). Naturally, combinations of the active substances mentioned can be immobilized. Preferably, an active substance is used which is soluble or dispersible in a hydrophobic phase.

In a preferred embodiment of the invention, the active substance is an odorous substance or fragrance. In the context of the invention, fragrance is understood to mean a compound which releases a particular desired odor. Fragrance is also understood to mean a mixture of compounds which is so composed that the odors of the different components of the mixture jointly release a pleasant or desired odor. Examples of compounds that can be used, alone or in combination, as fragrance are natural oils, vegetable and animal extracts, synthetic oils, alcohols, aldehydes, ketones,

esters, lactones, ethers, hydrocarbons, nitriles and other classes of chemical compounds. Fragrance can be used to impart to the environment, or other compounds or compositions, a modified, different or enhanced odor.

By immobilizing a fragrance in accordance with the invention, a highly favorable release pattern of the desired odor is accomplished. Additionally, by virtue of the high loading degrees that are feasible, a more intense or longer release pattern than before can be accomplished. Moreover, it has been found that the shelf life of fragrances is greatly extended by immobilizing them according to the invention.

In order to immobilize the active substance on the carrier material, a homogeneous mixture of the active substance and the carrier material in a liquid phase is formed. This can be done in different ways.

Depending on the nature of the carrier material and the active substance, by heating a mixture of the two, a liquid phase can be formed. In the liquid phase, a very homogeneous mixture can be obtained, for instance by stirring. Subsequently, by cooling, a solid phase can be formed, in which the active substance is immobilized on the carrier material.

It is also possible to form a solution or dispersion of the carrier material and the active substance in a suitable solvent, so that the liquid phase is formed by the solvent. By evaporating the solvent, the solid phase can be obtained, in which the active substance is immobilized on the carrier material. Suitable solvents can be obtained depending on the nature of the carrier material and the active substance. Preferably, the solvent has a relatively low boiling point. Examples of solvents that can be used are acetone, diethyl ether, dichloromethane, ethanol, methanol and isopropanol.

Incidentally, it is also possible to combine the two possibilities and to prepare a melt of the carrier material and the active substance in the presence of a small amount of a solvent, such as the solvents mentioned earlier.

In a preferred embodiment, small particles, such as microspheres, of immobilized active substance can be prepared by making use of the solvent evaporation method, known per se. It involves the preparation of an emulsion of the above-mentioned liquid phase. The additional liquid that is needed for that purpose is preferably water, so that an oil-in-water emulsion is obtained. If desired, a suitable emulsifier, for instance polyethylene glycol, can be used. This emulsion is subsequently dried, whereby the intended particles are formed. These can be isolated by, for instance, centrifugation.

In addition, it is possible to make use of the so-called double-emulsion technology as described in Dutch patent application 10.06444. This involves encapsulation of an active substance by preparing an oil-in-water emulsion of the active substance in a first hydrophobic phase and a solution or suspension of the carrier material in an aqueous starch dispersion or solution, which oil-in-water emulsion is subsequently incorporated in a second hydrophobic phase. When this technology is used in the context of the present invention, the active substance is included together with the carrier material in the first hydrophobic phase. As a result, it is possible to set the viscosity of this first hydrophobic phase, which makes the encapsulation simpler. Suitable materials for use as first and second hydrophobic phase can be simply found by one skilled in the art on the basis of the Dutch patent application mentioned in combination with his own expert knowledge.

According to another embodiment, a gaseous active substance is immobilized on the above-described carrier material. In order to achieve this, the carrier material can be employed in a liquid phase. This phase can be obtained by heating the carrier material or by dissolving or dispersing it in a suitable solvent. If desired, after immobilization of the gaseous active substance, the liquid phase can be converted to a solid phase by cooling or

removing the solvent. It is also possible to immobilize the gaseous active substance by contacting it with the carrier material in solid form.

According to the invention, it has been found possible to absorb active substances, in particular odorous substances. It has been found that the present carrier material is highly suitable for capturing odorous substances. Thus, for instance, fabric that has an unpleasant smell can be treated with the carrier material, as described above, so that the odorous substance spreading the undesired odor is immobilized on the carrier material. What is thus achieved is that the odor is reduced, at least is less perceptible. The odorous substance that is captured can be in the solid, liquid or gaseous phase. It has been found that when the odorous substance is in the gaseous form, it can be captured by the carrier material in solid form. In addition, the carrier material can be used in a liquid phase to absorb the odorous substance. After optional drying or cooling, the solid, immobilized active substance can be simply removed. Thus, the invention also relates to the use of an esterified polysaccharide for fixing or immobilizing an active substance, the active substance being preferably an odorous substance.

This embodiment of the invention can be suitably used for removing numerous unpleasant odors, for instance caused by body fluids, (armpit) deodorants, personal care products, such as (incontinence) diapers, sanitary napkins, panty-liners, tissues, (paper) napkins or towels, and toilet paper, air fresheners, space deodorants, cat litter. In a preferred embodiment, a product, such as (incontinence) diapers, sanitary napkins, panty-liners, tissues, paper napkins or towels, toilet paper or cat litter, can be provided with the carrier material according to the invention, so that in use the products spread less unpleasant odors.

The degree of loading that can be achieved according to the invention is partly dependent on the nature of the carrier material, the active substance and the application. Mostly, loading will be between 0.1 and 99%

by weight, in particular between 1 and 50% by weight, based on the total weight of dry matter of the carrier material.

If desired, the solid, immobilized active substance, which may or may not be modified as described above, can be processed to form a powder, for instance by grinding. The particle size of the powder can be selected depending on the intended application of the immobilized active substance. It is also possible to use the immobilized active substance in larger forms. Such forms can be obtained by the use of conventional polymer shaping techniques such as extrusion, including film and foil extrusion, injection molding, pressing or vacuum drawing.

In order to influence the processability and applicability of the immobilized active substance, a chemical or physical modification can be performed on the surface of the carrier material. Examples of suitable modifications are partial hydrolysis of the carrier material, crosslinking of the carrier material and ionization of the carrier material, and combinations thereof. It will be clear to one skilled in the art that a variety of modifications known per se are eligible under given circumstances. Preferably, only a part of the carrier material, preferably less than 5% by weight, more preferably less than 1% by weight, of the total amount of carrier material is modified.

Partial hydrolysis of the carrier material leads to the immobilized active substance acquiring a more hydrophilic character, which may be desirable when applications in aqueous medium are contemplated. The hydrolysis can be carried out, for instance, by suspending particles of the carrier material in water. Optionally, a small amount (0.1 - 2% by weight, based on the weight of the particles) of surfactant, such as sodium dodecylsulfate or an alkyl (poly)glucoside can be added. If desired, the hydrolysis can be accelerated by changing the pH of the suspension or raising the temperature. Preferably, work is done at a pH between 8 and 13 and a temperature between 20 and 40°C.

Crosslinking of the surface of the particles can be carried out to make the immobilized active substance less soluble in water. This may be desired after a partial hydrolysis or other modification has been carried out. When crosslinking is used in combination with a partial hydrolysis, an immobilized active substance is obtained which does not dissolve in water but can be very well incorporated in water, for instance in the form of a suspension. In addition, crosslinking leads to the active substance being retained particularly well by the carrier material. Crosslinking can be carried out by a reaction with a suitable crosslinking agent, such as trisodium phosphate or epichlorohydrin. To that end, for instance, a suspension is prepared of the particles in water, optionally in the presence of a small amount (0.1 - 2% by weight, based on the weight of the particles) of surfactant, such as sodium dodecylsulfate or an alkyl (poly)glucoside, to which the crosslinking agent is added in an amount of 0.5-3% by weight, based on the weight of the particles. Preferably, a small amount (0.5 - 5% by weight, based on the weight of the particles) of a base, for instance NaOH or KOH, is added. Other examples of possible crosslinking reactions are described in R.L. Whistler, E.F. Paschall, "Starch Chemistry and Technology", vol. 1 & 2 (1965), Academic Press Inc.

By providing positively or negatively charged groups, the interaction of the immobilized active substance with the environment can be set. What can thus be achieved is, for instance, that the immobilized active substance adheres well to other materials, such as fabric. In addition, the dispersibility of the immobilized active substance can be positively influenced. The provision of positively or negatively charged groups at the surface can in principle be carried out in any known manner for introducing charged groups into a polysaccharide material. Examples of suitable methods are described inter alia in R.L. Whistler, E.F. Paschall, "Starch Chemistry and Technology", vol. 1 & 2 (1965), Academic Press Inc.

Quaternary ammonium groups and carboxyl or phosphate groups are preferred.

The active substance can be released to a target environment by chemical, physical or enzymatic influences. Normally, these influences will (partially) break down or modify the carrier material, such that the active substance is liberated. The active substance can, for instance, be released into the digestive tract under the influence of the prevailing conditions in the various organs (pH, enzymes). Optionally, the sensitivity of carrier material can be adapted by starting from a different esterified polysaccharide derivative. In laundering agents, the release can be promoted by temperature increase or, again, by pH or enzyme influences. On or in cultivated soil or potting soil, the release can be accomplished by hydrolysis or action of salts. In reaction mixtures, the release can also be accomplished by the influence of, for instance, electric current or pH adjustment.

The immobilized active substance can be used in various applications. Examples include washing agents, fabric softeners, cleaning agents (such as cleaners, detergents, disinfectants, washing-up agents, dish-washing agents, rinsing agents, bleaching agents, and toilet cleaners), fabric conditioners, fabric sprays, ironing aids, tumble dryer additions, optical whiteners, odor masking agents, personal care products, fertilizers, foods, flavors, pharmaceutical agents, tissues, cosmetics (such as perfumes, colognes, bath and shower products, shampoos, hair conditioning products, skin care products, sun screens, creams, lotions, aerosols, and soaps), soil improvers, plant protection agents (against fungi, bacteria, insects, mites, nematodes and the like), covering layers or coatings, paints, inks, organic reactants (hydrogen peroxide), catalysis, and diagnostics.

The invention will now be further elucidated in and by the following examples.

Example 1 (immobilization of a fragrance on a carrier material)

A. Paselli acetate (10 g) is dissolved in a mixture of fragrance (5 g) and acetone (5 g), optionally with heating (50°C). Next, the volatile solvent acetone is removed by heating the material at 80°C. After cooling, a hard brittle material having a fragrance loading of about 33% by weight is obtained. The material is ground, optionally cryogenically, to form a powder.

B. Paselli acetate (10 g) is dissolved in a mixture of fragrance (5 g) and acetone (5 g), optionally with heating (50°C). Next, a thin film is formed of Paselli acetate/fragrance by pouring the solution onto glass and allowing the volatile solvent acetone to evaporate.

C. Paselli acetate (10 g) is dissolved or suspended in fragrance (5 g) and heated in a closed reactor at 105°C for 2 hours. After cooling, a hard brittle material having a fragrance loading of about 33% is obtained. The material is ground, optionally cryogenically, to form a powder.

D. Paselli acetate powder (500 mg) is brought into a saturated atmosphere of fragrance. Depending on the absorption time and the temperature, the loading can be set, see also Fig. 4. The material is ground, optionally cryogenically, to form a powder.

E. Cellulose acetate (10 g) is dissolved in a mixture of fragrance (5 g) and acetone (5 g), optionally with heating (50°C). Next, the volatile solvent acetone is removed by heating the material at 80°C. After cooling, a hard brittle material having a fragrance loading of about 33% by weight is obtained. The material is ground, optionally cryogenically, to form a powder.

Example 2 (chemical modifications on surface of the immobilized active substance)

A. A combination of hydrolysis and crosslinking is carried out in water. Paselli acetate/fragrance powder (10 g) is suspended in 50 g water with 20 mg SDS (sodium dodecylsulfate). Next, 0.2-0.4 g NaOH is added and 0.1 g epichlorohydrin. The suspension is stirred at room temperature for 18 hours. The material is subsequently washed and separated by centrifugation.

B. Anionization: Paselli acetate/fragrance powder (10 g) is suspended in 50 g water with 20 mg SDS (sodium dodecylsulfate). A solution of 0.1 g NaOH in 1 ml water is added, followed by stirring for 18 hours. Next, NaBr (0.1 g), Tempo (20 mg, 2,2,6,6-tetramethyl-piperidine-l-oxide) and sodium hypochlorite solution (10g; 4g Cl+/100g) are added. The pH of the reaction is held at 10 for 30 minutes. The material is washed and separated by centrifugation.

C. Anionization: Paselli acetate/fragrance powder (15 g) is suspended in 250 g water with 20 mg SDS (sodium dodecylsulfate). Next, TSTP (trisodium triphosphate; 2.0 g) is added while the pH is held at 12 for 1-2 hours. The material is washed and separated by centrifugation.

D. Cationization: Paselli acetate/fragrance powder (5 g) is suspended in 50 g water with 10 mg SDS (sodium dodecylsulfate). Next, glycidyltrimethyl-ammonium chloride (GMAC; 0.2 g), epichlorohydrin (0.05 g) and a solution of 0.25 g NaOH in 1 g water are added. The suspension is stirred at room temperature for 18 hours. The material is washed and separated by centrifugation.

Example 3 (release behavior of fragrances)

A. Figure 1 gives the release profiles of a yes- (a) and no- (b) immobilized fragrance mixture (ACB 56SE) applied to fabric. The figure clearly shows differing release behavior. The fragrance mixture is immobilized on a carrier material consisting of Paselli acetate having a DS of 3.

B. Figure 2 gives the release profiles of three immobilized fragrances, viz., Linalool (a), Tilianol Super (b) and Hydroxycitronellal (c). The figure clearly shows that the fragrances exhibit a mutually different release behavior. The fragrances are immobilized on a carrier material consisting of Paselli acetate having a DS of 3.

C. Figure 3 gives the release profiles of Jasmacyclene, immobilized on different carrier materials consisting of Paselli acetate with a DS of 1.0 (a), 1.7 (b) and 3 (c). The figure clearly shows that the active substance exhibits a lower release rate at a higher degree of substitution.

Example 4 (absorption behavior of carrier material)

Figure 4 gives the absorption behavior at room temperature for the fragrance Frutalone on a powdered Paselli acetate carrier material with a DS of 3. The amount of carrier material (0.1 gram (a) or 0.5 gram (b)) that is present in the saturated fragrance vapor has an influence on the absorption rate.

Example 5 (adherence of immobilized fragrance to fabric during washing)

Paselli acetate/Tonalid powder (DS = 3; loading = 33%) is suspended in water in the presence of fabric (cotton). Washing is done at pH 10.4; T = 60°C for 1 hour. Thereupon, the fabric is rinsed with water and dried. The

fragrance present on the fabric is extracted by means of dichloroethane and analyzed by means of gas chromatography. Figure 5 shows the adhesion, i.e. the percentage of the total fragrance that has adhered to the fabric during washing, for a few different modifications and a control experiment with normal, i.e. non-immobilized, Tonalid. The figure shows that the adherence of the fragrance increases due to the above-described immobilization and modifications.

In Figure 5 there are shown, from left to right: *blank* (= control, i.e. non-immobilized Tonalid); *neutral* (= immobilized Tonalid); *anionic* (= immobilized Tonalid, with anionized surface); *cationic* (= immobilized Tonalid, with cationized surface).

Example 6 (solvent evaporation method)

Two grams of acetylated starch (DS = 3) were dissolved, together with 1 gram of the fragrance frutalone, in 10 ml dichloromethane, analogously to the procedure of Example 1. The mixture obtained was emulsified in 200 ml water, utilizing 3% by weight of polyethylene glycol (Mw = 1,000) as emulsifier. An ultrasonic probe was used (50 output; 2 min.). Solvent evaporation was subsequently carried out while stirring (top-stirrer; 500 rpm) for 2 hours at room temperature and ambient pressure. The thus obtained microspheres were collected by centrifugation (27,000 g; 15 min.). Thereafter the particles were dried in air at room temperature and an air humidity of 30% RH. Measurement with GC showed the loading to be 28 wt. %.

CLAIMS

1. A method for immobilizing an active substance, wherein a mixture is prepared of the active substance and a carrier material in a liquid phase, whereafter the liquid phase is converted to a solid phase, the carrier material being an esterified polysaccharide.

2. A method according to claim 1, wherein the liquid phase is obtained by mixing and heating the active substance and the carrier material until a homogeneous liquid mixture is obtained, and wherein the solid phase is obtained by cooling.

3. A method according to claim 1, wherein the liquid phase is obtained by dissolving or dispersing the active substance and the carrier material in a solvent, and wherein the solid phase is obtained by evaporating the solvent.

4. A method according to claim 3, wherein the solvent is selected from the group of acetone, dichloromethane, diethyl ether, ethanol, methanol and isopropanol.

5. A method according to claims 1-4, wherein the liquid phase is emulsified in a liquid and wherein small particles are formed of the immobilized active substance by evaporating the liquid.

6. A method according to claim 5, wherein the liquid is water.

7. A method according to claim 1, wherein the liquid phase is a double emulsion, which is formed by preparing an oil-in-water emulsion of the active substance in a first hydrophobic phase and a solution or suspension of the carrier material in an aqueous starch solution or starch dispersion and including this oil-in-water emulsion in a second hydrophobic phase, and wherein the solid phase is formed by crosslinking the starch and removing the second hydrophobic phase.

8. A method for immobilizing an active substance, wherein the active substance is contacted in gaseous form with a carrier material in solid

phase or a liquid phase, the carrier material being an esterified polysaccharide.

9. A method according to any one of the preceding claims, wherein the esterified polysaccharide is an esterified starch, cellulose, alginate, pectin, or a derivative thereof.

10. A method according to any one of the preceding claims, wherein the polysaccharide is esterified with an acetate group, a propionate group, a butyrate group, an alkyl succinate group, wherein the alkyl group contains from 1 to 16 carbon atoms, a benzoate group, or an ester group which is derived from a carboxylic acid having 1 to 18 carbon atoms.

11. A method according to any one of the preceding claims, wherein the polysaccharide has a degree of substitution (DS) between 0.05 and a DS corresponding to a virtually complete substitution.

12. A method according to any one of the preceding claims, wherein the active substance is selected from the group of medicines, plant protection agents, paramagnetic substances, catalysts, organic reactants, cosmetic active substances, colorants, fragrances, flavors, and nutrients.

13. A method according to any one of the preceding claims, wherein the immobilized active substance is formed into a powder.

14. A method according to any one of the preceding claims, wherein the immobilized active substance is processed by the use of polymer shaping techniques, such as extrusion, injection molding, pressing or vacuum drawing.

15. A method according to any one of the preceding claims, wherein a physical or chemical modification is performed on the surface of the immobilized active substance.

16. An immobilized active substance obtainable by a method according to any one of the preceding claims.

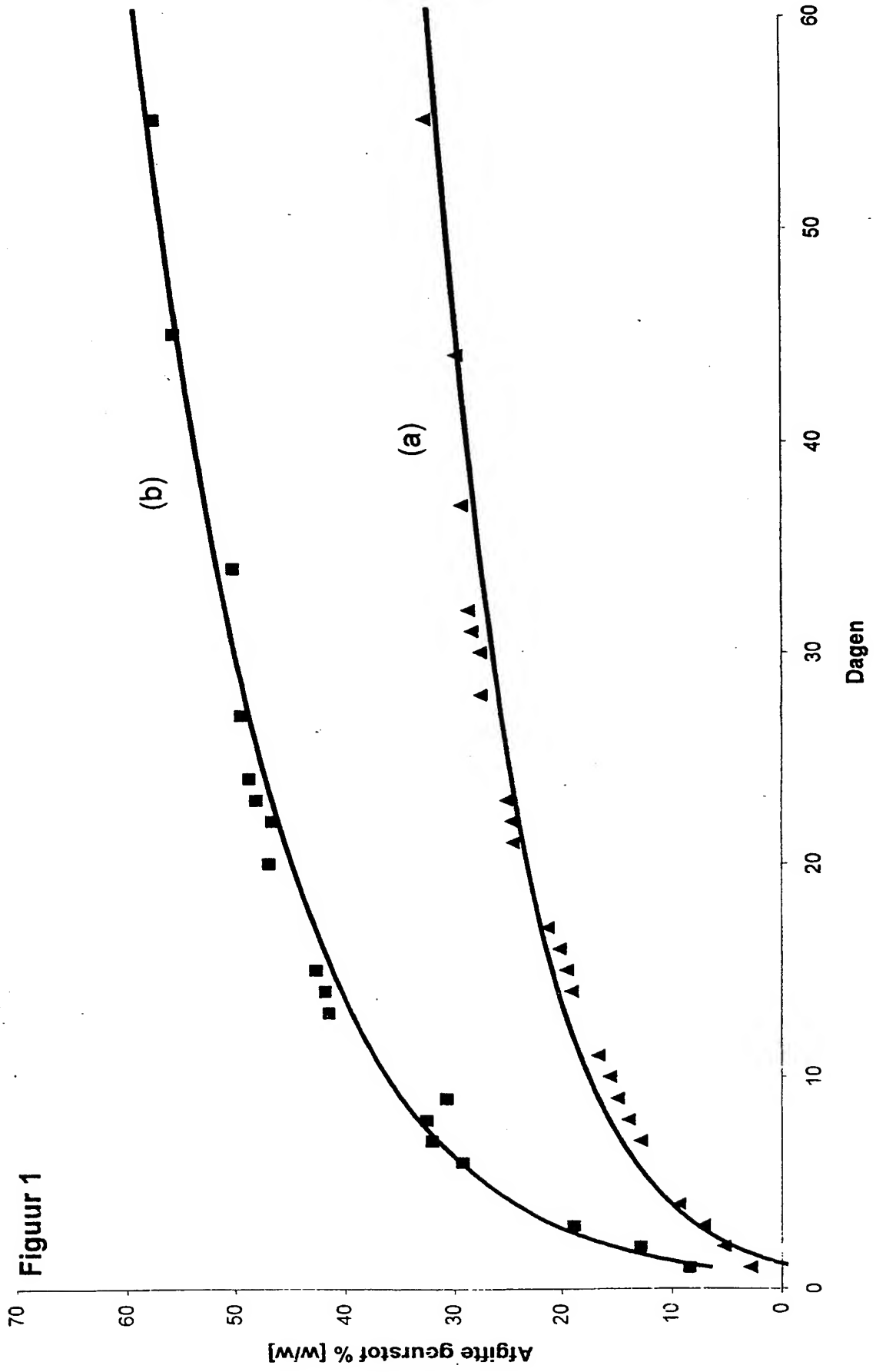
17. Use of an immobilized active substance according to claim 16 in a detergent, fabric softener, cleaning agent, soap, shampoo, fabric conditioner,

fabric spray, ironing aid, tumble dryer addition, optical whitener, odor masking agent, personal care product, fertilizer, food, flavor, pharmaceutical, tissue, cosmetics, soil improvers, plant protection agents, covering layer or coating, paint, ink, in organic synthesis, diagnostics or agriculture.

18. Use of an esterified polysaccharide for fixing or immobilizing an active substance.

19. Use according to claim 18, wherein the active substance is an odorous substance.

20. Use according to claim 19 for reducing an odor.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(a)
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30
40
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Dagen
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30
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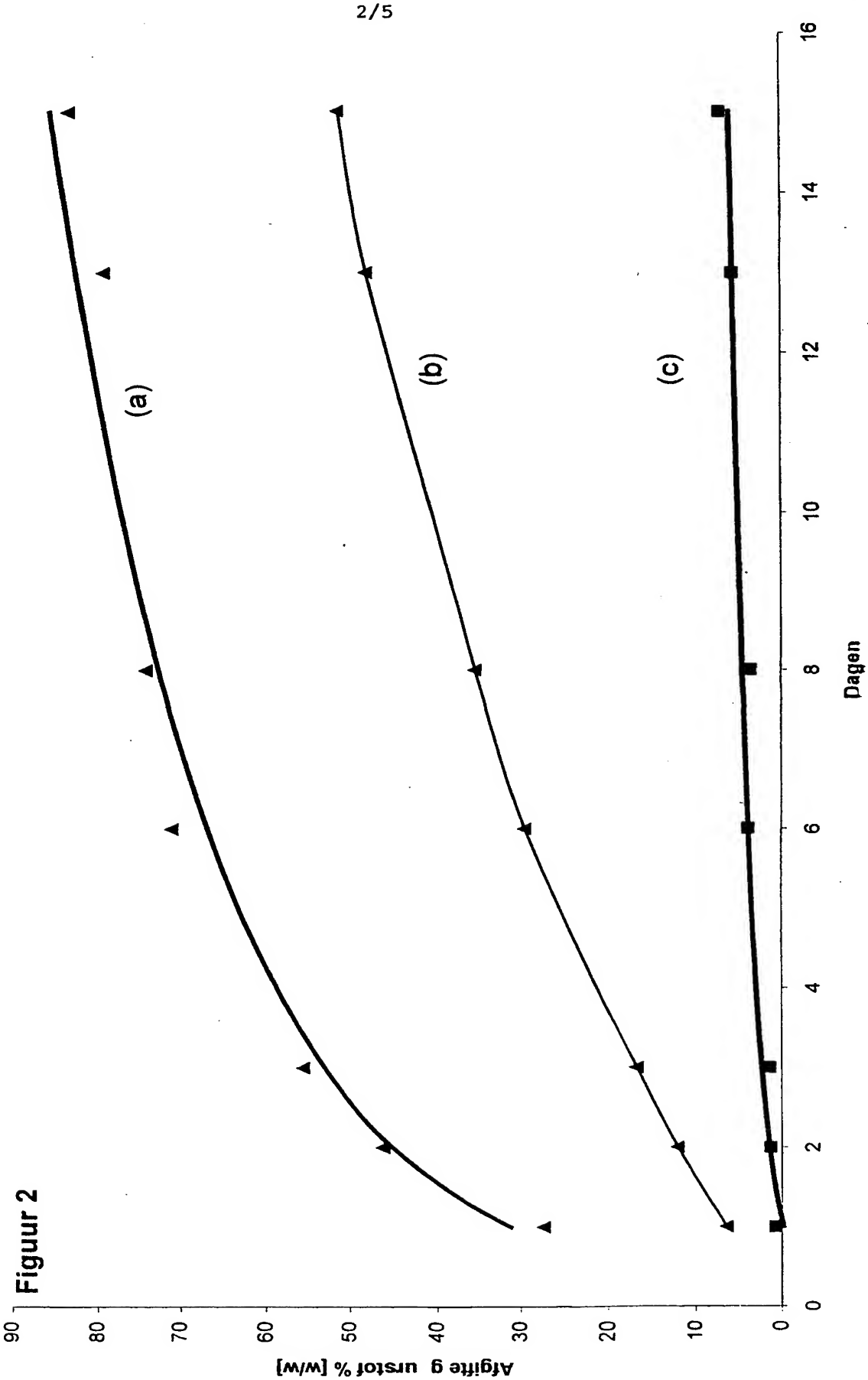
60

Figuur 1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Dagen
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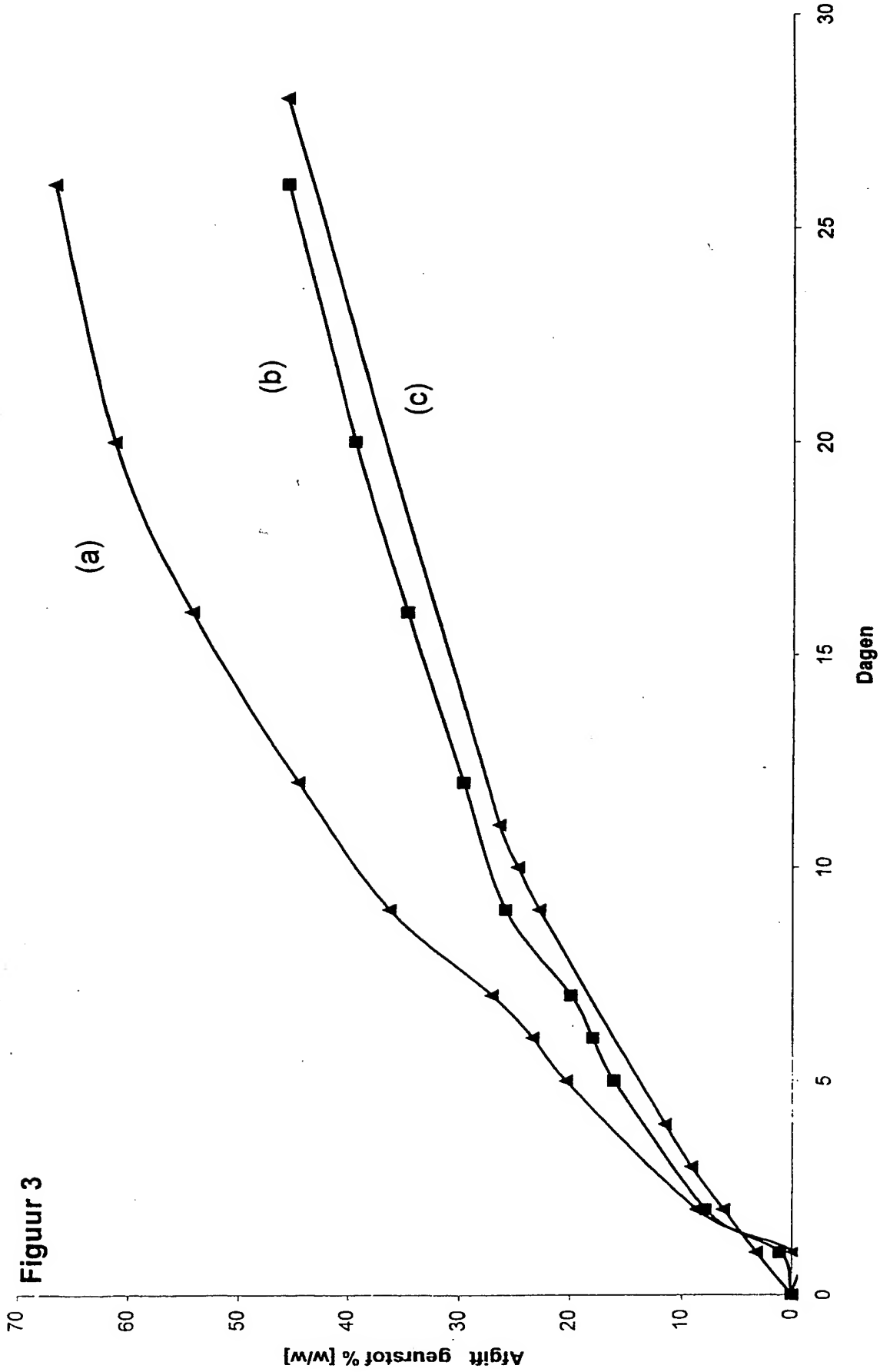
Figuur 2


(a)
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Dagen
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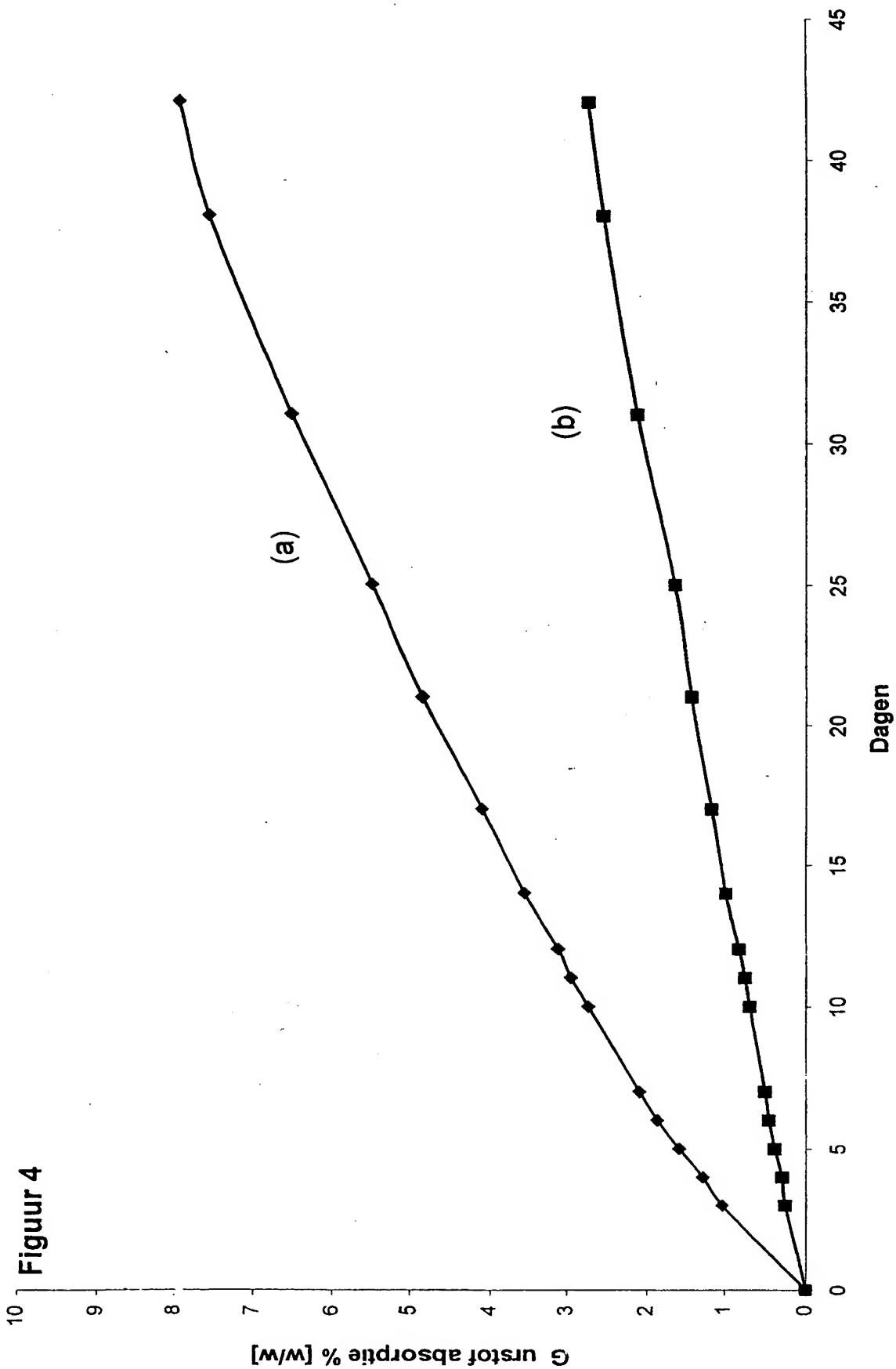
25
30

Figuur 3


(a)
(b)
Dagen
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15
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35
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1
2
3
4
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6
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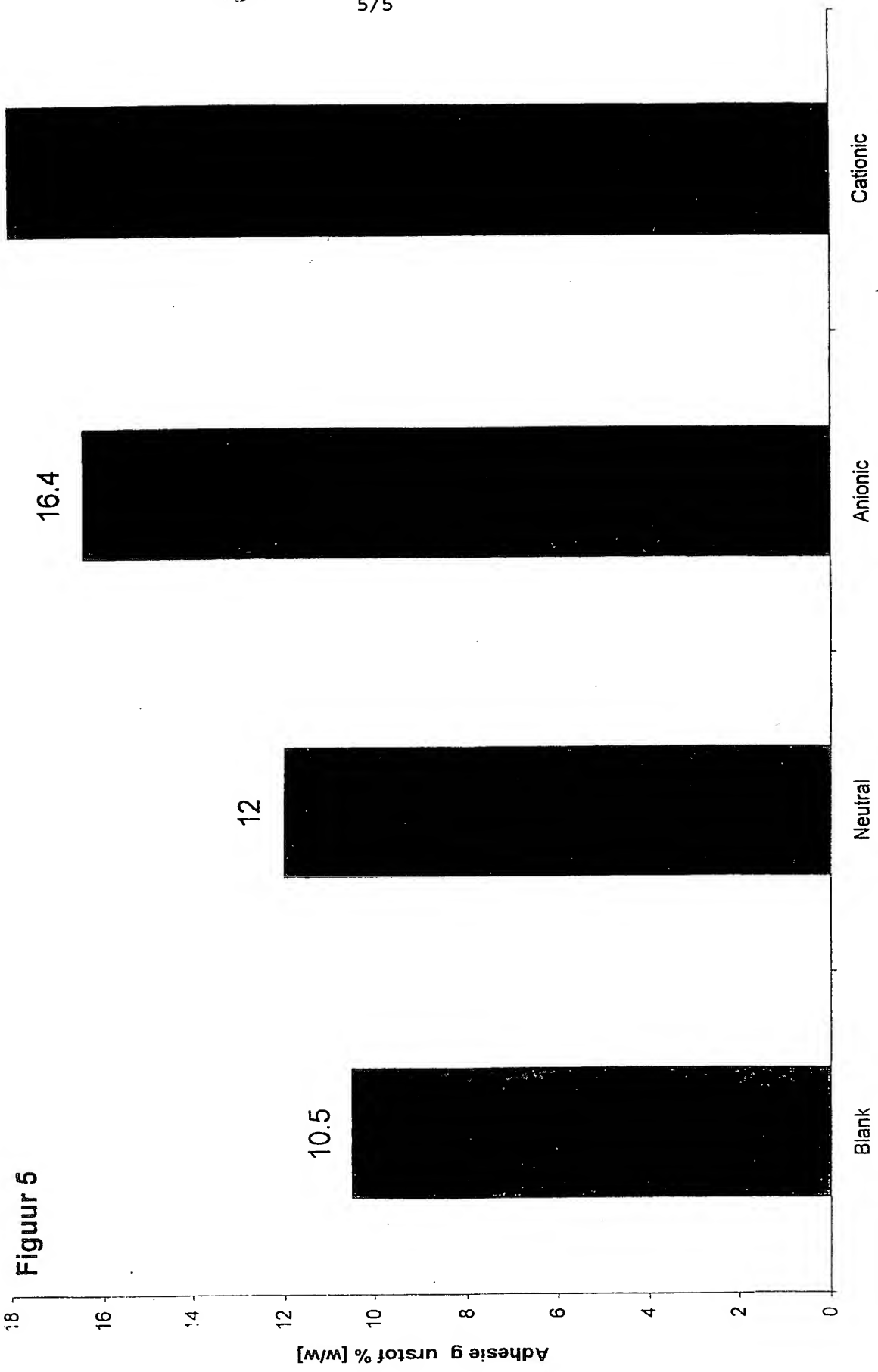
9
10

Figuur 4


Adhesie g urstof % [w/w]
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2
4
6
8
10
12
14
16
18
10.5
12
16.4
18
Blank
Neutral
Anionic
Cationic

Figuur 5

PATENT COOPERATION TREATY

KB

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

PRINS, A. W.
c/o VEREENIGDE
Nieuwe Parklaan 97
NL-2587 BN The Hague
PAYS-BAS

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TERMIJN
16 NOV 2001
Beantwoord | ... gezonden
Voorl.
Def.
MAP

PCT

NRF2 28-2-2002

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	14.11.2001
Applicant's or agent's file reference P49634PC00	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NL00/00603	30/08/2000	30/08/1999

Applicant
PFW AROMA CHEMICALS B.V. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Aperribay, I Tel.+49 89 2399-8154

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P49634PC00		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NL00/00603	30/08/2000	30/08/1999
International Patent Classification (IPC) or national classification and IPC A01N25/24		
Applicant PFW AROMA CHEMICALS B.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14/03/2001	14.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Radke, M Telephone No. +49 89 2399 8677

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL00/00603

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-15	as originally filed				

Claims, No.:

1-17	as received on	01/11/2001	with letter of	01/11/2001

Drawings, sheets:

1/5-5/5	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4-8, 13 and 17
	No:	Claims	1-3, 9-12 and 14-16
Inventive step (IS)	Yes:	Claims	
	No:	Claims	4-8, 13 and 17
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations
   see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Cited literature

(a) Reference is made to the following documents:

D1: US-A-3 455 838
D2: EP-A-0 901 786
D3: WO-A-99 01 214
D4: GB-A-2229 364

(b) The documents **D1**, **D2**, **D3** and **D4** were not cited in the international search report. Document **D1** is cited on page 2, lines 15-23 of the present description; **D3** is equivalent to **NL-C-1 006 444** cited on page 2, lines 4-14 in the present description. Copies of **D1, D2, D3** and **D3** were appended to the written opinion.

(c) In the following arguments, page or column A, lines B to C will be cited as A/B-C.

2. Preliminary remarks

Unclear and relative terms in the claims "prevent the invention from being unambiguously distinguished from the prior art ..." (PCT Examination Guidelines, III-4.5 and 4.5a).

The term "not or poorly soluble in water" inserted in **claim 1** is such an unclear and relative term since there is no clear cut boundary between "poorly soluble" and "readily soluble". Furthermore, the solubility of polysaccharides in water is highly dependent on temperature so that a certain polysaccharide may be readily soluble in cold water but almost insoluble in hot water.

Present **claim 1** does, however, not clearly specify the degree of solubility and the temperature at which it is to determined.

Therefore, this feature was not taken into account when assessing novelty and inventive step.

3. Novelty

(a) Document **D1** discloses a method for encapsulating water-insoluble substances by
(1) dispersing an acid ester of dextrinised starch with a substituted dicarboxylic acid in water,
(2) emulsifying the water-insoluble substance in said dispersion and drying the emulsion, e.g. by spray drying (see claims 1 and 4).
In the examples, the ester of dextrin with octenyl succinic acid was dispersed in water, lemon oil (examples I to III) was emulsified therein, and the emulsion thus formed was spray dried.

(b) Octenyl succinic acid forms "an ester group derived from carboxylic acid having from 1 to 18 carbon atoms" when reacted with dextrin.

(c) Lemon oil is a fragrance.

(d) The subject-matter of **claims 1, 2** (see the temperature difference indicated at 5/30-32), **3, 9-12** (spray drying is a very common method for drying polymer dispersions), **14, 15** (see 2/18-21), **and 16** is not novel in view of **D1**.

4. Inventive step

(a) The subject-matter of **claims 4 to 8, 13 and 17** is not disclosed in **D1** or any other other cited document. It is thus novel.

(b) The additional features of the following claims are, however, obvious in view of the following parts of the literature cited:

Claim 4:	**D2**, 11/45-12/22;
claims 5 to 7:	**D3**, claims 1, 2 and 11 and the examples;

claim 8: **D4**, test example 2 on page 19, where a gas is absorbed on a cellulose acetate fibre.

claim 13: **D3**, claim 14.

Consequently, the subject-matter of **claims 4 to 8 and 13** is not based on an inventive step.

(c) Document **D1** discloses at 2/18-21 the use of the encapsulated products in "..., soaps, detergents, bleaches and cleansers." Such compositions are normally used for reducing odours (such as those caused by sweat). Therefore, the subject-matter of **claim 17** is not based on an inventive step.

NEW CLAIMS

1. A method for immobilizing a fragrance, wherein a mixture is prepared of the fragrance and a carrier material in a liquid phase, whereafter the liquid phase is converted to a solid phase, the carrier material being an esterified polysaccharide which is esterified to such a degree that it is not or poorly soluble in water with an acetate group, a propionate group, a butyrate group, an alkyl succinate group, in which the alkyl group contains from 1 to 16 carbon atoms, a benzoate group, or an ester group derived from carboxylic acid having from 1 to 18 carbon atoms.

2. A method according to claim 1, wherein the liquid phase is obtained by mixing and heating the fragrance and the carrier material until a homogeneous liquid mixture is obtained, and wherein the solid phase is obtained by cooling.

3. A method according to claim 1, wherein the liquid phase is obtained by dissolving or dispersing the fragrance and the carrier material in a solvent, and wherein the solid phase is obtained by evaporating the solvent.

4. A method according to claim 3, wherein the solvent is selected from the group of acetone, dichloromethane, diethyl ether, ethanol, methanol and isopropanol.

5. A method according to claims 1-4, wherein the liquid phase is emulsified in a liquid and wherein small particles are formed of the immobilized fragrance by evaporating the liquid.

6. A method according to claim 5, wherein the liquid is water.

7. A method according to claim 1, wherein the liquid phase is a double emulsion, which is formed by preparing an oil-in-water emulsion of the fragrance in a first hydrophobic phase and a solution or suspension of the carrier material in an aqueous starch solution or starch dispersion and including this oil-in-water emulsion in a second hydrophobic phase, and wherein the solid phase is formed by crosslinking the starch and removing the second hydrophobic phase.

8. A method for immobilizing a fragrance, wherein the fragrance is contacted in gaseous form with a carrier material in solid phase or a liquid phase, the carrier material being an esterified polysaccharide according to claim 1.

9. A method according to any one of the preceding claims, wherein the esterified polysaccharide is an esterified starch, cellulose, alginate, pectin, or a derivative thereof.

10. A method according to any one of the preceding claims, wherein the polysaccharide has a degree of substitution (DS) between 0.05 and a DS corresponding to a virtually complete substitution.

11. A method according to any one of the preceding claims, wherein the immobilized fragrance is formed into a powder.

12. A method according to any one of the preceding claims, wherein the immobilized fragrance is processed by the use of polymer shaping techniques, such as extrusion, injection molding, pressing or vacuum drawing.

13. A method according to any one of the preceding claims, wherein a physical or chemical modification is performed on the surface of the immobilized fragrance.

14. An immobilized fragrance obtainable by a method according to any one of the preceding claims.

15. Use of an immobilized fragrance according to claim 14 in a detergent, fabric softener, cleaning agent, soap, shampoo, fabric conditioner, fabric spray, ironing aid, tumble dryer addition, optical whitener, odor masking agent, personal care product, fertilizer, food, flavor, pharmaceutical, tissue, cosmetics, soil improvers, plant protection agents, covering layer or coating, paint, ink, in organic synthesis, diagnostics or agriculture.

16. Use of an esterified polysaccharide according to claim 1 for fixing or immobilizing a fragrance.

17. Use according to claim 16 for reducing an odor.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

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WO 01/020985 A1

(54) Title: IMMOBILIZATION OF ACTIVE SUBSTANCES

(57) Abstract: The invention relates to a method for immobilizing an active substance, wherein a mixture is prepared of the active substance and a carrier material in a liquid phase, whereafter the liquid phase is converted to a solid phase, the carrier material being an esterified polysaccharide. The invention further relates to the use of an esterified polysaccharide for fixing or immobilizing active substances, in particular odorous substances.

Title: Immobilization of active substances

This invention relates to a method for immobilizing active substances.

In the literature, different methods are known for the immobilization of active substances. The purpose of the immobilization is normally to achieve a slowed and/or controlled release of the active substance. Substances that are used as carrier material on which the active substances are immobilized vary in nature. To be mentioned by way of example are synthetic polymers and biopolymers such as starch or alginates.

International patent application 89/03674 discloses a method for preparing microspheres by suspending an active substance, such as paramagnetic particles, in a starch solution, crosslinking the starch with a phosphate, and emulsifying the starch in a hydrophobic medium before or after crosslinking.

European patent application 0 930 334 discloses a polysaccharide conjugate which is capable of binding cellulose. The conjugate is based on a polysaccharide, which is not modified, and a particle that carries a perfume. The particle is preferably a porous silica particle, into which the perfume can penetrate through diffusion.

U.S. Patent 5,667,803 relates to the use of a starch acetate as auxiliary substance in pharmaceutical compacted compositions, mainly tablets. Depending on the degree of substitution (DS) of the starch acetate, it is to be used as disintegrator, filler, binder, or agent for regulating the release of an active substance from a tablet. No mention is made of the immobilization of an active substance on a starch acetate. Accordingly, the starch acetate itself cannot, in the application of this publication, be regarded as carrier material.

International patent application 93/02712 discloses a method in which an oil-in-water emulsion of a soluble starch fraction and an organic

solvent, such as dichloromethane, is prepared, to which a dehydrating agent such as an alcohol is added. The thus obtained microspheres are fixed by retrogradation of the starch, which must therefore have a high amylose content.

Dutch patent application 10.06444 proposes an improvement of the above-mentioned immobilization methods. According to the method described therein, microparticles consisting of an effective substance in a starch envelope are prepared by preparing an oil-in-water emulsion of the effective substance in a hydrophobic phase and starch in water, including this emulsion in a second hydrophobic phase, and subsequently crosslinking the starch. Optionally, the second hydrophobic phase can eventually be removed. A disadvantage of this method is that with different types of effective substances it has been found that high degrees of loading of the effective substance in the microsphere are not feasible.

U.S. Patents 3,455,838 and 5,354,559 and the British Patent Specification all relate to the encapsulation of active substances with water-soluble or shortened starches, which are optionally substituted. The degree of substitution (DS) of the starches described is low in each case. The encapsulation in each case takes place from an emulsion or with the aid of a spray-drying technique. A disadvantage of the systems described is their water-sensitivity. When used in an aqueous medium, for instance during a washing process, the capsules will easily disintegrate, so that the active substance is released into the water at an undesired time.

Surprisingly, it has presently been found that the above-mentioned disadvantages can be obviated by using a specific carrier material for the immobilization of an active substance. The specific carrier material is an esterified polysaccharide. The invention thus relates to a method for immobilizing an active substance, wherein a mixture is prepared of the active substance and a carrier material in a liquid phase, whereafter the

liquid phase is converted to a solid phase, the carrier material being an esterified polysaccharide.

According to the invention, highly stable systems are obtained. This is understood to mean that it is accomplished that an active substance which is immobilized according to the invention is substantially not released under undesired conditions and is substantially released only under desired conditions. Thus, according to the invention, a particularly favorable slowed-release profile can be set. This is also understood to mean that through the immobilization the active substance is protected, so that the chance of breakdown of the active substance through physical or chemical influences is reduced considerably. Thus, an active substance immobilized according to the invention will have a prolonged shelf life. Further, according to the invention, it has been found possible to load a carrier material with very large amounts of active substance.

Further, it is a great advantage of the manner of immobilization according to the invention that it can be effected very simply. Virtually no (complex) operations need to be performed to obtain the stable system referred to.

As used in this text, the term "immobilized active substance" refers to a complex of an active substance and a carrier material.

As said, the carrier material that is used according to the invention is an esterified polysaccharide. Examples of suitable polysaccharides are starch, cellulose, alginates, pectin and combinations thereof. Preferably, the polysaccharide is starch or cellulose, starch being particularly preferred. With esterified starch, very high loading degrees are feasible. In principle, the starch can originate from any natural starch source. Suitable, among others, is starch coming from potatoes, corn, wheat, and tapioca. Preferably, granular starch is used. Optionally, the starch can be wholly or partly gelatinized.

To obtain the desired esterified polysaccharide, it is possible to start from the native polysaccharide or from a derivative thereof. Suitable derivatives in this connection are, for instance, (partially) hydrolyzed polysaccharides, oxidized polysaccharides, ionized (both cationic and anionic) and etherified polysaccharides. Incidentally, it will be clear that the reaction that is performed starting from native polysaccharide to obtain any one of the derivatives mentioned can also be performed with the polysaccharide already esterified.

The esterified polysaccharide is preferably biodegradable. In the context of the invention, a biodegradable material is understood to mean a material that has the property of being broken down within a relatively short time into substances that are preferably soluble in water and non-toxic. The breakdown can take place *inter alia* through hydrolytic cleavage, under the influence of light, air, water and/or microorganisms occurring in nature.

The esterification proper can be carried out in any known manner. The polysaccharide can, for instance, be subjected to a reaction with an acid anhydride, which provides the desired ester group, in aqueous, slightly alkaline medium. Examples of suitable esterification reactions are to be found in R.L. Whistler, E.F. Paschall, "Starch Chemistry and Technology", vol. 1 & 2 (1965), Academic Press Inc. The esterification is preferably carried out so as to yield a degree of substitution (DS) at which the esterified polysaccharide is not soluble or poorly soluble in water. In view of this criterion, the desired degree of substitution depends on the nature of the ester group. When the ester group is relatively non-polar, the value of the degree of substitution can be between 0.05 and a DS corresponding to a complete substitution, and preferably, in particular, between 0.1 and 2.7. In the case of a less non-polar ester group, such as an acetate group, the degree of substitution is preferably slightly higher, viz. between 0.3 and 3, preferably between 0.3 and 2.7. It has been found that the release rate of

hydrophilic active substances is higher at a relatively high DS, while the release rate of hydrophobic active substances is higher at a relatively low DS.

Suitable ester groups that can be introduced are *inter alia* acetate groups, propionate groups, butyrate groups, alkyl succinate groups, in which the alkyl group contains from 1 to 16 carbon atoms, benzoate groups, and ester groups which are derived from carboxylic acids having from 1 to 18 carbon atoms, such as saturated and monounsaturated or polyunsaturated fatty acids. Preferably, an acetate ester of a polysaccharide is used, because an active substance can be immobilized with it in a particularly stable manner.

The active substance which is immobilized according to the invention can be selected from *inter alia* medicines (for instance hormones, antiinflammatory agents, insulin, chemotherapeuticals, antibiotics, vaccines and the like), plant protection agents (such as atachloride), paramagnetic substances, catalysts, organic reactants, pheromones, lures, cosmetic actives, washing active substances, disinfectants, fabric conditioning actives, hair conditioning actives, colorants, fragrance, flavor, and nutrients (for instance vitamins, fats, proteins, peptides, etc.). Naturally, combinations of the active substances mentioned can be immobilized. Preferably, an active substance is used which is soluble or dispersible in a hydrophobic phase.

In a preferred embodiment of the invention, the active substance is an odorous substance or fragrance. In the context of the invention, fragrance is understood to mean a compound which releases a particular desired odor. Fragrance is also understood to mean a mixture of compounds which is so composed that the odors of the different components of the mixture jointly release a pleasant or desired odor. Examples of compounds that can be used, alone or in combination, as fragrance are natural oils, vegetable and animal extracts, synthetic oils, alcohols, aldehydes, ketones,

esters, lactones, ethers, hydrocarbons, nitriles and other classes of chemical compounds. Fragrance can be used to impart to the environment, or other compounds or compositions, a modified, different or enhanced odor.

By immobilizing a fragrance in accordance with the invention, a highly favorable release pattern of the desired odor is accomplished. Additionally, by virtue of the high loading degrees that are feasible, a more intense or longer release pattern than before can be accomplished. Moreover, it has been found that the shelf life of fragrances is greatly extended by immobilizing them according to the invention.

In order to immobilize the active substance on the carrier material, a homogeneous mixture of the active substance and the carrier material in a liquid phase is formed. This can be done in different ways.

Depending on the nature of the carrier material and the active substance, by heating a mixture of the two, a liquid phase can be formed. In the liquid phase, a very homogeneous mixture can be obtained, for instance by stirring. Subsequently, by cooling, a solid phase can be formed, in which the active substance is immobilized on the carrier material.

It is also possible to form a solution or dispersion of the carrier material and the active substance in a suitable solvent, so that the liquid phase is formed by the solvent. By evaporating the solvent, the solid phase can be obtained, in which the active substance is immobilized on the carrier material. Suitable solvents can be obtained depending on the nature of the carrier material and the active substance. Preferably, the solvent has a relatively low boiling point. Examples of solvents that can be used are acetone, diethyl ether, dichloromethane, ethanol, methanol and isopropanol.

Incidentally, it is also possible to combine the two possibilities and to prepare a melt of the carrier material and the active substance in the presence of a small amount of a solvent, such as the solvents mentioned earlier.

In a preferred embodiment, small particles, such as microspheres, of immobilized active substance can be prepared by making use of the solvent evaporation method, known per se. It involves the preparation of an emulsion of the above-mentioned liquid phase. The additional liquid that is needed for that purpose is preferably water, so that an oil-in-water emulsion is obtained. If desired, a suitable emulsifier, for instance polyethylene glycol, can be used. This emulsion is subsequently dried, whereby the intended particles are formed. These can be isolated by, for instance, centrifugation.

In addition, it is possible to make use of the so-called double-emulsion technology as described in Dutch patent application 10.06444. This involves encapsulation of an active substance by preparing an oil-in-water emulsion of the active substance in a first hydrophobic phase and a solution or suspension of the carrier material in an aqueous starch dispersion or solution, which oil-in-water emulsion is subsequently incorporated in a second hydrophobic phase. When this technology is used in the context of the present invention, the active substance is included together with the carrier material in the first hydrophobic phase. As a result, it is possible to set the viscosity of this first hydrophobic phase, which makes the encapsulation simpler. Suitable materials for use as first and second hydrophobic phase can be simply found by one skilled in the art on the basis of the Dutch patent application mentioned in combination with his own expert knowledge.

According to another embodiment, a gaseous active substance is immobilized on the above-described carrier material. In order to achieve this, the carrier material can be employed in a liquid phase. This phase can be obtained by heating the carrier material or by dissolving or dispersing it in a suitable solvent. If desired, after immobilization of the gaseous active substance, the liquid phase can be converted to a solid phase by cooling or

removing the solvent. It is also possible to immobilize the gaseous active substance by contacting it with the carrier material in solid form.

According to the invention, it has been found possible to absorb active substances, in particular odorous substances. It has been found that the present carrier material is highly suitable for capturing odorous substances. Thus, for instance, fabric that has an unpleasant smell can be treated with the carrier material, as described above, so that the odorous substance spreading the undesired odor is immobilized on the carrier material. What is thus achieved is that the odor is reduced, at least is less perceptible. The odorous substance that is captured can be in the solid, liquid or gaseous phase. It has been found that when the odorous substance is in the gaseous form, it can be captured by the carrier material in solid form. In addition, the carrier material can be used in a liquid phase to absorb the odorous substance. After optional drying or cooling, the solid, immobilized active substance can be simply removed. Thus, the invention also relates to the use of an esterified polysaccharide for fixing or immobilizing an active substance, the active substance being preferably an odorous substance.

This embodiment of the invention can be suitably used for removing numerous unpleasant odors, for instance caused by body fluids, (armpit) deodorants, personal care products, such as (incontinence) diapers, sanitary napkins, panty-liners, tissues, (paper) napkins or towels, and toilet paper, air fresheners, space deodorants, cat litter. In a preferred embodiment, a product, such as (incontinence) diapers, sanitary napkins, panty-liners, tissues, paper napkins or towels, toilet paper or cat litter, can be provided with the carrier material according to the invention, so that in use the products spread less unpleasant odors.

The degree of loading that can be achieved according to the invention is partly dependent on the nature of the carrier material, the active substance and the application. Mostly, loading will be between 0.1 and 99%

by weight, in particular between 1 and 50% by weight, based on the total weight of dry matter of the carrier material.

If desired, the solid, immobilized active substance, which may or may not be modified as described above, can be processed to form a powder, for instance by grinding. The particle size of the powder can be selected depending on the intended application of the immobilized active substance. It is also possible to use the immobilized active substance in larger forms. Such forms can be obtained by the use of conventional polymer shaping techniques such as extrusion, including film and foil extrusion, injection molding, pressing or vacuum drawing.

In order to influence the processability and applicability of the immobilized active substance, a chemical or physical modification can be performed on the surface of the carrier material. Examples of suitable modifications are partial hydrolysis of the carrier material, crosslinking of the carrier material and ionization of the carrier material, and combinations thereof. It will be clear to one skilled in the art that a variety of modifications known per se are eligible under given circumstances. Preferably, only a part of the carrier material, preferably less than 5% by weight, more preferably less than 1% by weight, of the total amount of carrier material is modified.

Partial hydrolysis of the carrier material leads to the immobilized active substance acquiring a more hydrophilic character, which may be desirable when applications in aqueous medium are contemplated. The hydrolysis can be carried out, for instance, by suspending particles of the carrier material in water. Optionally, a small amount (0.1 - 2% by weight, based on the weight of the particles) of surfactant, such as sodium dodecylsulfate or an alkyl (poly)glucoside can be added. If desired, the hydrolysis can be accelerated by changing the pH of the suspension or raising the temperature. Preferably, work is done at a pH between 8 and 13 and a temperature between 20 and 40°C.

Crosslinking of the surface of the particles can be carried out to make the immobilized active substance less soluble in water. This may be desired after a partial hydrolysis or other modification has been carried out. When crosslinking is used in combination with a partial hydrolysis, an immobilized active substance is obtained which does not dissolve in water but can be very well incorporated in water, for instance in the form of a suspension. In addition, crosslinking leads to the active substance being retained particularly well by the carrier material. Crosslinking can be carried out by a reaction with a suitable crosslinking agent, such as trisodium phosphate or epichlorohydrin. To that end, for instance, a suspension is prepared of the particles in water, optionally in the presence of a small amount (0.1 - 2% by weight, based on the weight of the particles) of surfactant, such as sodium dodecylsulfate or an alkyl (poly)glucoside, to which the crosslinking agent is added in an amount of 0.5-3% by weight, based on the weight of the particles. Preferably, a small amount (0.5 - 5% by weight, based on the weight of the particles) of a base, for instance NaOH or KOH, is added. Other examples of possible crosslinking reactions are described in R.L. Whistler, E.F. Paschall, "Starch Chemistry and Technology", vol. 1 & 2 (1965), Academic Press Inc.

By providing positively or negatively charged groups, the interaction of the immobilized active substance with the environment can be set. What can thus be achieved is, for instance, that the immobilized active substance adheres well to other materials, such as fabric. In addition, the dispersibility of the immobilized active substance can be positively influenced. The provision of positively or negatively charged groups at the surface can in principle be carried out in any known manner for introducing charged groups into a polysaccharide material. Examples of suitable methods are described inter alia in R.L. Whistler, E.F. Paschall, "Starch Chemistry and Technology", vol. 1 & 2 (1965), Academic Press Inc.

Quaternary ammonium groups and carboxyl or phosphate groups are preferred.

The active substance can be released to a target environment by chemical, physical or enzymatic influences. Normally, these influences will (partially) break down or modify the carrier material, such that the active substance is liberated. The active substance can, for instance, be released into the digestive tract under the influence of the prevailing conditions in the various organs (pH, enzymes). Optionally, the sensitivity of carrier material can be adapted by starting from a different esterified polysaccharide derivative. In laundering agents, the release can be promoted by temperature increase or, again, by pH or enzyme influences. On or in cultivated soil or potting soil, the release can be accomplished by hydrolysis or action of salts. In reaction mixtures, the release can also be accomplished by the influence of, for instance, electric current or pH adjustment.

The immobilized active substance can be used in various applications. Examples include washing agents, fabric softeners, cleaning agents (such as cleaners, detergents, disinfectants, washing-up agents, dish-washing agents, rinsing agents, bleaching agents, and toilet cleaners), fabric conditioners, fabric sprays, ironing aids, tumble dryer additions, optical whiteners, odor masking agents, personal care products, fertilizers, foods, flavors, pharmaceutical agents, tissues, cosmetics (such as perfumes, colognes, bath and shower products, shampoos, hair conditioning products, skin care products, sun screens, creams, lotions, aerosols, and soaps), soil improvers, plant protection agents (against fungi, bacteria, insects, mites, nematodes and the like), covering layers or coatings, paints, inks, organic reactants (hydrogen peroxide), catalysis, and diagnostics.

The invention will now be further elucidated in and by the following examples.

Example 1 (immobilization of a fragrance on a carrier material)

A. Paselli acetate (10 g) is dissolved in a mixture of fragrance (5 g) and acetone (5 g), optionally with heating (50°C). Next, the volatile solvent acetone is removed by heating the material at 80°C. After cooling, a hard brittle material having a fragrance loading of about 33% by weight is obtained. The material is ground, optionally cryogenically, to form a powder.

B. Paselli acetate (10 g) is dissolved in a mixture of fragrance (5 g) and acetone (5 g), optionally with heating (50°C). Next, a thin film is formed of Paselli acetate/fragrance by pouring the solution onto glass and allowing the volatile solvent acetone to evaporate.

C. Paselli acetate (10 g) is dissolved or suspended in fragrance (5 g) and heated in a closed reactor at 105°C for 2 hours. After cooling, a hard brittle material having a fragrance loading of about 33% is obtained. The material is ground, optionally cryogenically, to form a powder.

D. Paselli acetate powder (500 mg) is brought into a saturated atmosphere of fragrance. Depending on the absorption time and the temperature, the loading can be set, see also Fig. 4. The material is ground, optionally cryogenically, to form a powder.

E. Cellulose acetate (10 g) is dissolved in a mixture of fragrance (5 g) and acetone (5 g), optionally with heating (50°C). Next, the volatile solvent acetone is removed by heating the material at 80°C. After cooling, a hard brittle material having a fragrance loading of about 33% by weight is obtained. The material is ground, optionally cryogenically, to form a powder.

Exampl 2 (chemical modifications on surface of the immobilized active substance)

A. A combination of hydrolysis and crosslinking is carried out in water. Paselli acetate/fragrance powder (10 g) is suspended in 50 g water with 20 mg SDS (sodium dodecylsulfate). Next, 0.2-0.4 g NaOH is added and 0.1 g epichlorohydrin. The suspension is stirred at room temperature for 18 hours. The material is subsequently washed and separated by centrifugation.

B. Anionization: Paselli acetate/fragrance powder (10 g) is suspended in 50 g water with 20 mg SDS (sodium dodecylsulfate). A solution of 0.1 g NaOH in 1 ml water is added, followed by stirring for 18 hours. Next, NaBr (0.1 g), Tempo (20 mg, 2,2,6,6-tetramethyl-piperidine-l-oxide) and sodium hypochlorite solution (10g; 4g Cl+/100g) are added. The pH of the reaction is held at 10 for 30 minutes. The material is washed and separated by centrifugation.

C. Anionization: Paselli acetate/fragrance powder (15 g) is suspended in 250 g water with 20 mg SDS (sodium dodecylsulfate). Next, TSTP (trisodium triphosphate; 2.0 g) is added while the pH is held at 12 for 1-2 hours. The material is washed and separated by centrifugation.

D. Cationization: Paselli acetate/fragrance powder (5 g) is suspended in 50 g water with 10 mg SDS (sodium dodecylsulfate). Next, glycidyltrimethyl-ammonium chloride (GMAC; 0.2 g), epichlorohydrin (0.05 g) and a solution of 0.25 g NaOH in 1 g water are added. The suspension is stirred at room temperature for 18 hours. The material is washed and separated by centrifugation.

Example 3 (release behavior of fragrances)

A. Figure 1 gives the release profiles of a yes- (a) and no- (b) immobilized fragrance mixture (ACB 56SE) applied to fabric. The figure clearly shows differing release behavior. The fragrance mixture is immobilized on a carrier material consisting of Paselli acetate having a DS of 3.

B. Figure 2 gives the release profiles of three immobilized fragrances, viz., Linalool (a), Tilianol Super (b) and Hydroxycitronellal (c). The figure clearly shows that the fragrances exhibit a mutually different release behavior. The fragrances are immobilized on a carrier material consisting of Paselli acetate having a DS of 3.

C. Figure 3 gives the release profiles of Jasmacyclene, immobilized on different carrier materials consisting of Paselli acetate with a DS of 1.0 (a), 1.7 (b) and 3 (c). The figure clearly shows that the active substance exhibits a lower release rate at a higher degree of substitution.

Example 4 (absorption behavior of carrier material)

Figure 4 gives the absorption behavior at room temperature for the fragrance Frutalone on a powdered Paselli acetate carrier material with a DS of 3. The amount of carrier material (0.1 gram (a) or 0.5 gram (b)) that is present in the saturated fragrance vapor has an influence on the absorption rate.

Example 5 (adherence of immobilized fragrance to fabric during washing)

Paselli acetate/Tonalid powder (DS = 3; loading = 33%) is suspended in water in the presence of fabric (cotton). Washing is done at pH 10.4; T = 60°C for 1 hour. Thereupon, the fabric is rinsed with water and dried. The

fragrance present on the fabric is extracted by means of dichloroethane and analyzed by means of gas chromatography. Figure 5 shows the adhesion, i.e. the percentage of the total fragrance that has adhered to the fabric during washing, for a few different modifications and a control experiment with normal, i.e. non-immobilized, Tonalid. The figure shows that the adherence of the fragrance increases due to the above-described immobilization and modifications.

In Figure 5 there are shown, from left to right: *blank* (= control, i.e. non-immobilized Tonalid); *neutral* (= immobilized Tonalid); *anionic* (= immobilized Tonalid, with anionized surface); *cationic* (= immobilized Tonalid, with cationized surface).

Example 6 (solvent evaporation method)

Two grams of acetylated starch (DS = 3) were dissolved, together with 1 gram of the fragrance frutalone, in 10 ml dichloromethane, analogously to the procedure of Example 1. The mixture obtained was emulsified in 200 ml water, utilizing 3% by weight of polyethylene glycol (Mw = 1,000) as emulsifier. An ultrasonic probe was used (50 output; 2 min.). Solvent evaporation was subsequently carried out while stirring (top-stirrer; 500 rpm) for 2 hours at room temperature and ambient pressure. The thus obtained microspheres were collected by centrifugation (27,000 g; 15 min.). Thereafter the particles were dried in air at room temperature and an air humidity of 30% RH. Measurement with GC showed the loading to be 28 wt. %.

CLAIMS

1. A method for immobilizing an active substance, wherein a mixture is prepared of the active substance and a carrier material in a liquid phase, whereafter the liquid phase is converted to a solid phase, the carrier material being an esterified polysaccharide.

2. A method according to claim 1, wherein the liquid phase is obtained by mixing and heating the active substance and the carrier material until a homogeneous liquid mixture is obtained, and wherein the solid phase is obtained by cooling.

3. A method according to claim 1, wherein the liquid phase is obtained by dissolving or dispersing the active substance and the carrier material in a solvent, and wherein the solid phase is obtained by evaporating the solvent.

4. A method according to claim 3, wherein the solvent is selected from the group of acetone, dichloromethane, diethyl ether, ethanol, methanol and isopropanol.

5. A method according to claims 1-4, wherein the liquid phase is emulsified in a liquid and wherein small particles are formed of the immobilized active substance by evaporating the liquid.

6. A method according to claim 5, wherein the liquid is water.

7. A method according to claim 1, wherein the liquid phase is a double emulsion, which is formed by preparing an oil-in-water emulsion of the active substance in a first hydrophobic phase and a solution or suspension of the carrier material in an aqueous starch solution or starch dispersion and including this oil-in-water emulsion in a second hydrophobic phase, and wherein the solid phase is formed by crosslinking the starch and removing the second hydrophobic phase.

8. A method for immobilizing an active substance, wherein the active substance is contacted in gaseous form with a carrier material in solid

phase or a liquid phase, the carrier material being an esterified polysaccharide.

9. A method according to any one of the preceding claims, wherein the esterified polysaccharide is an esterified starch, cellulose, alginate, pectin, or a derivative thereof.

10. A method according to any one of the preceding claims, wherein the polysaccharide is esterified with an acetate group, a propionate group, a butyrate group, an alkyl succinate group, wherein the alkyl group contains from 1 to 16 carbon atoms, a benzoate group, or an ester group which is derived from a carboxylic acid having 1 to 18 carbon atoms.

11. A method according to any one of the preceding claims, wherein the polysaccharide has a degree of substitution (DS) between 0.05 and a DS corresponding to a virtually complete substitution.

12. A method according to any one of the preceding claims, wherein the active substance is selected from the group of medicines, plant protection agents, paramagnetic substances, catalysts, organic reactants, cosmetic active substances, colorants, fragrances, flavors, and nutrients.

13. A method according to any one of the preceding claims, wherein the immobilized active substance is formed into a powder.

14. A method according to any one of the preceding claims, wherein the immobilized active substance is processed by the use of polymer shaping techniques, such as extrusion, injection molding, pressing or vacuum drawing.

15. A method according to any one of the preceding claims, wherein a physical or chemical modification is performed on the surface of the immobilized active substance.

16. An immobilized active substance obtainable by a method according to any one of the preceding claims.

17. Use of an immobilized active substance according to claim 16 in a detergent, fabric softener, cleaning agent, soap, shampoo, fabric conditioner,

fabric spray, ironing aid, tumble dryer addition, optical whitener, odor masking agent, personal care product, fertilizer, food, flavor, pharmaceutical, tissue, cosmetics, soil improvers, plant protection agents, covering layer or coating, paint, ink, in organic synthesis, diagnostics or agriculture.

18. Use of an esterified polysaccharide for fixing or immobilizing an active substance.

19. Use according to claim 18, wherein the active substance is an odorous substance.

20. Use according to claim 19 for reducing an odor.

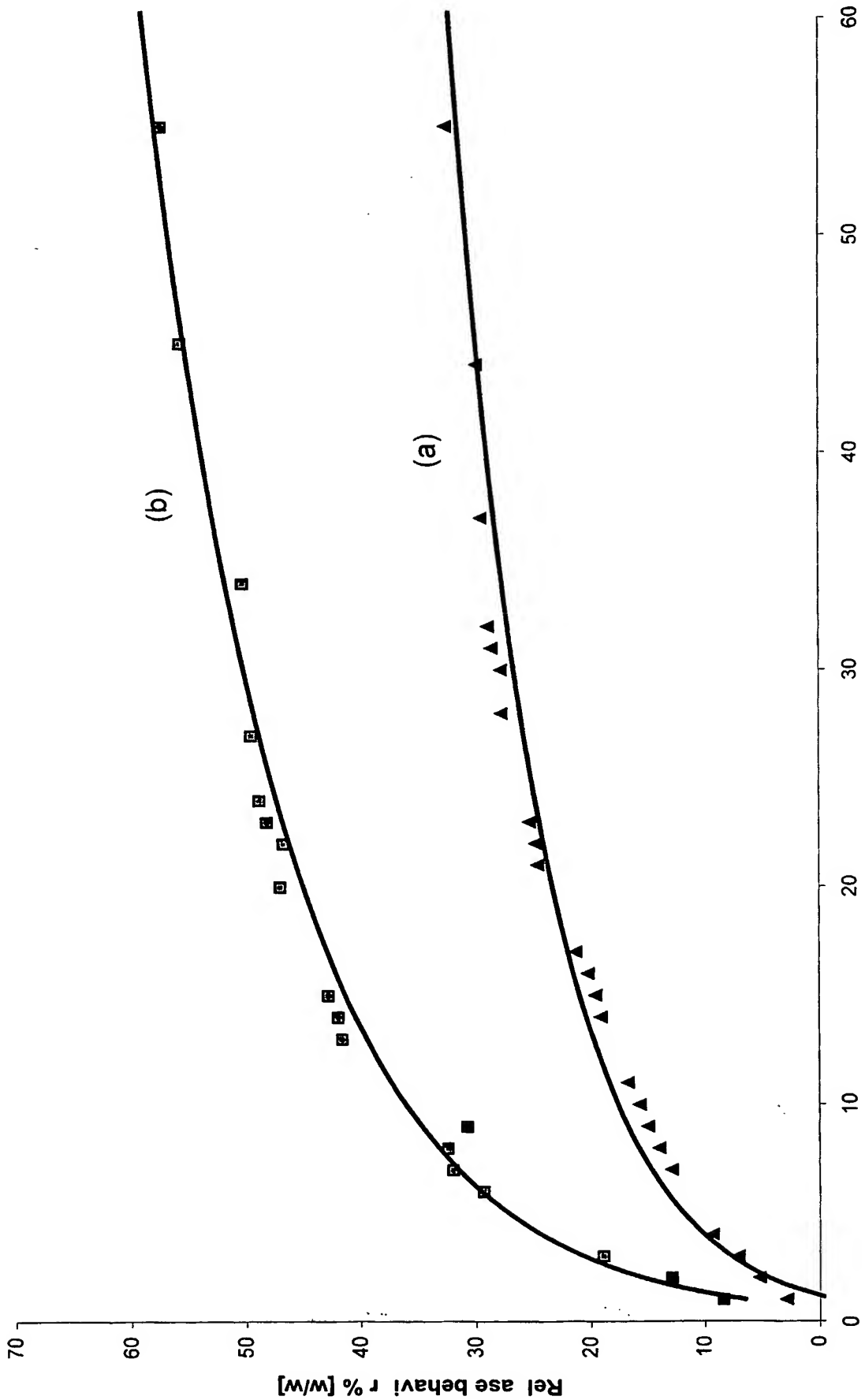

Fig. 1

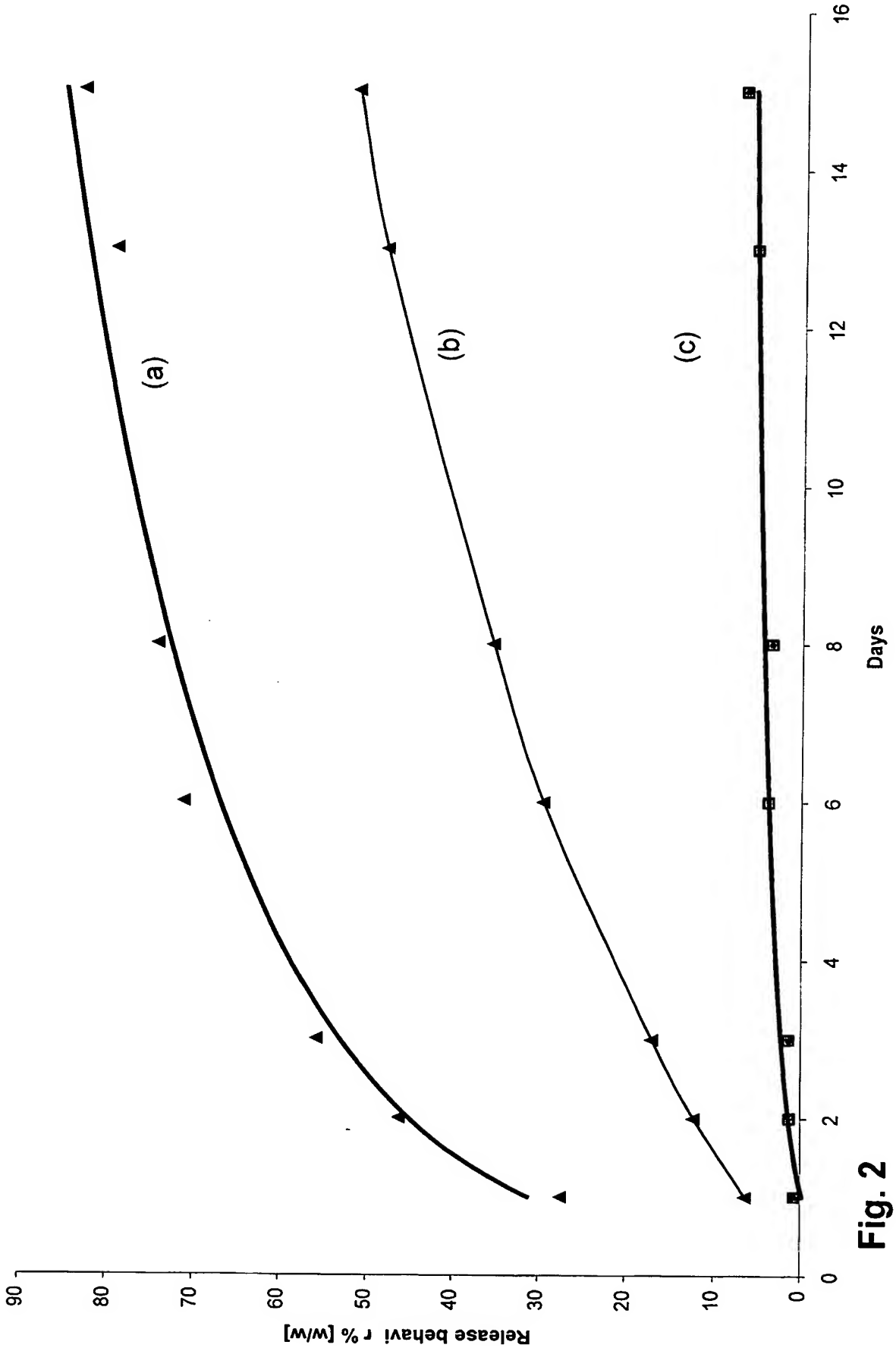
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Fig. 2

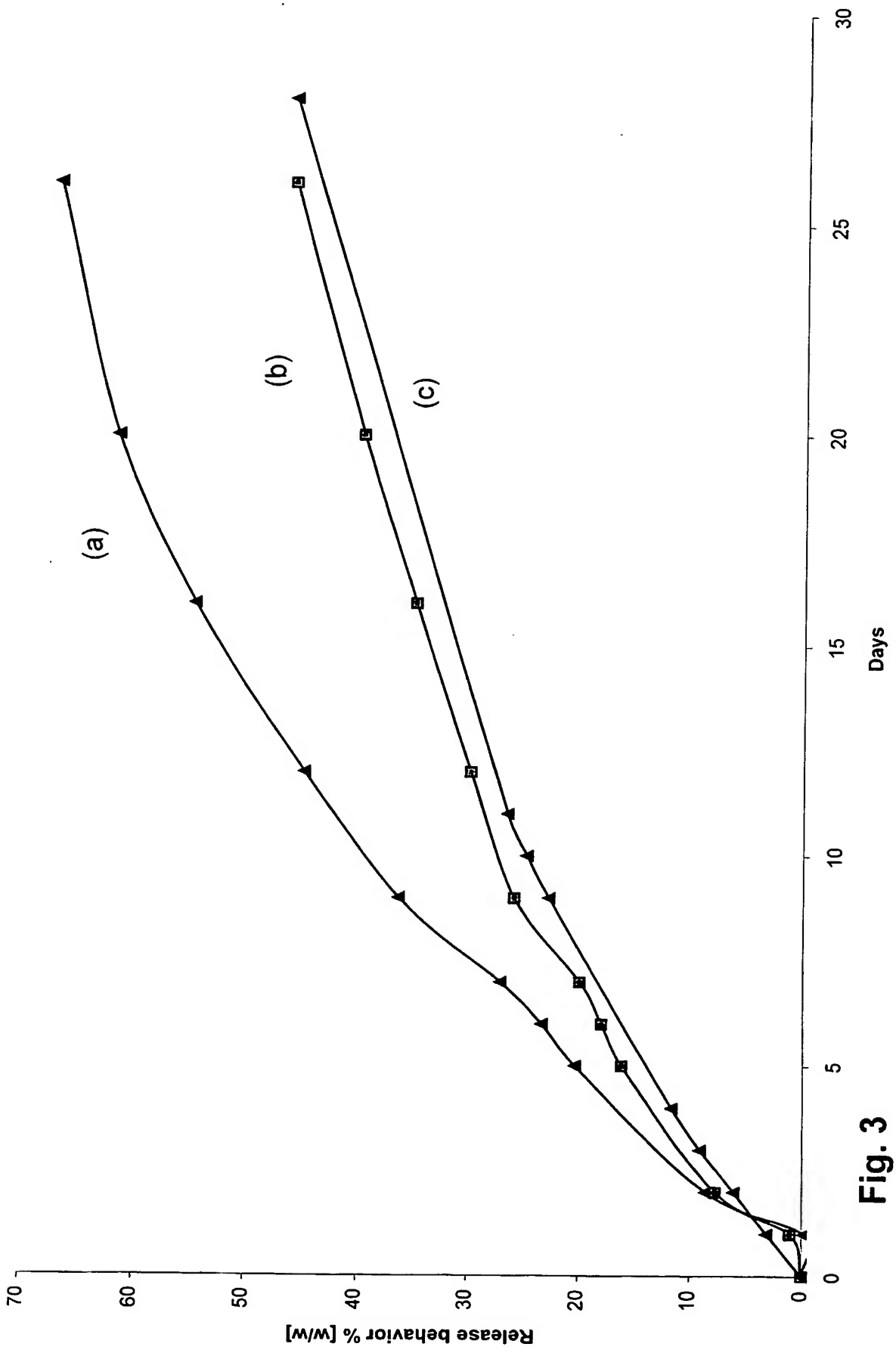
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Fig. 3

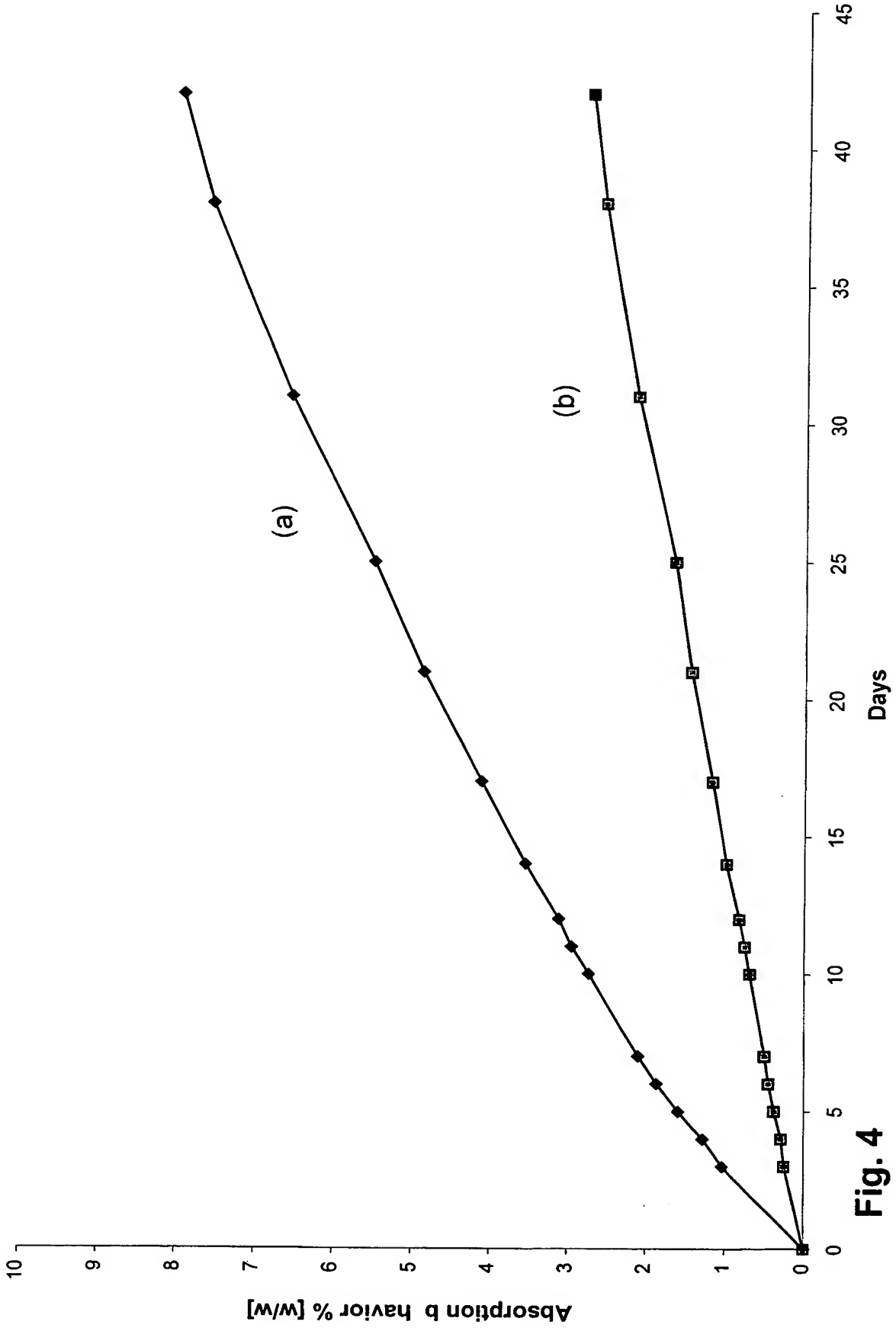
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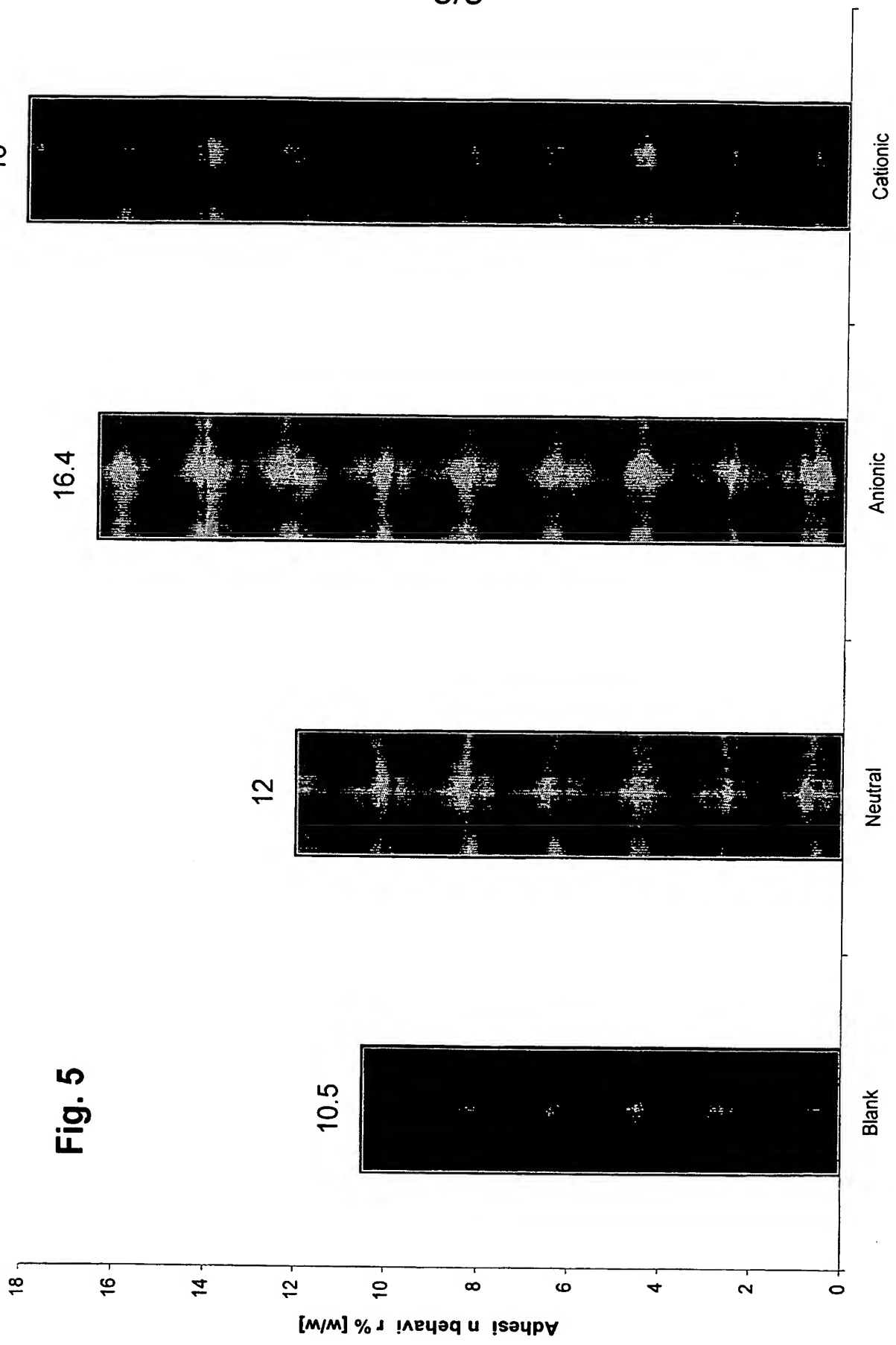
Fig. 4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Neutral
Anionic
Cationic

Fig. 5

INTERNATIONAL SEARCH REPORT

International Application No
PCT/NL 00/00603

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A01N25/24 A61K7/46 C08L1/10 C08L3/06 C11D3/50
D06M15/11 B01J20/26 B01J13/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 512 693 A (DELTA BIOTECHNOLOGY LTD) 11 November 1992 (1992-11-11) page 3, line 51 -page 4, line 9	1-20
X	US 4 230 687 A (SAIR LOUIS ET AL) 28 October 1980 (1980-10-28) the whole document	1-20
X	WO 92 11083 A (REDDING BRUCE K JR) 9 July 1992 (1992-07-09) page 11, line 7 -page 12, line 15; table 2	1-20

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 December 2000	27/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Reedijk, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/NL 00/00603

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 81, no. 22, 2 December 1974 (1974-12-02) Columbus, Ohio, US; abstract no. 140875m, page 289; XP002137793 abstract & JP 49 062623 A (FUJI PHOTO FILM) 18 June 1974 (1974-06-18) ---	1-7,9-16
A	EP 0 691 398 A (UNILEVER NV ;UNILEVER PLC (GB)) 10 January 1996 (1996-01-10) page 5, line 1 - line 27 -----	1-20

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/NL 00/00603

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0512693 A	11-11-1992	AT 194082 T	15-07-2000
		AU 655016 B	01-12-1994
		AU 1589192 A	17-11-1992
		AU 691196 B	14-05-1998
		AU 7448394 A	22-12-1994
		CA 2083260 A	11-10-1992
		CN 1066977 A	16-12-1992
		DE 69231195 D	03-08-2000
		EP 0533886 A	31-03-1993
		EP 0681843 A	15-11-1995
		EP 0972526 A	19-01-2000
		FI 925600 A	09-12-1992
		WO 9218164 A	29-10-1992
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		HK 1006538 A	05-03-1999
		HU 62805 A	28-06-1993
		IL 101564 A	20-06-1999
		JP 11128232 A	18-05-1999
		JP 2865866 B	08-03-1999
		KR 129861 B	09-04-1998
		MX 9201694 A	01-02-1993
		NZ 242328 A	22-12-1994
		RU 2109521 C	27-04-1998
		US 5993805 A	30-11-1999
		US 6022525 A	08-02-2000
		US 5518709 A	21-05-1996
		ZA 9202636 A	30-12-1992
US 4230687 A	28-10-1980	NONE	
WO 9211083 A	09-07-1992	US 4978483 A	18-12-1990
		AU 2551088 A	18-04-1989
		AU 620571 B	20-02-1992
		BR 8807221 A	17-10-1989
		DK 259189 A	27-07-1989
		EP 0336949 A	18-10-1989
		FI 892581 A	26-05-1989
		GB 2222982 A,B	28-03-1990
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		KR 9105190 B	23-07-1991
		NO 892149 A	21-07-1989
		WO 8902814 A	06-04-1989
		US 5271881 A	21-12-1993
		CN 1039540 A	14-02-1990
		ES 2013874 A	01-06-1990
		GR 89100195 A	31-01-1990
		IL 89526 A	01-12-1992
		MX 166283 B	28-12-1992
		PT 90081 A	10-11-1989
JP 49062623 3 A		NONE	
EP 0691398 A	10-01-1996	CA 2153360 A	09-01-1996

REPLACED BY ART 34 AMDT

14

PATENT COOPERATION TREATY

PCT

REC'D 16 NOV 2001
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P49634PC00		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NL00/00603	30/08/2000	30/08/1999
International Patent Classification (IPC) or national classification and IPC A01N25/24		
Applicant PFW AROMA CHEMICALS B.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14/03/2001	14.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Radke, M Telephone No. +49 89 2399 8677

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL00/00603

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-15	as originally filed				

Claims, No.:

1-17	as received on	01/11/2001	with letter of	01/11/2001	

Drawings, sheets:

1/5-5/5	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4-8, 13 and 17
	No:	Claims	1-3, 9-12 and 14-16
Inventive step (IS)	Yes:	Claims	
	No:	Claims	4-8, 13 and 17
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations
see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Cited literature

(a) Reference is made to the following documents:

D1: US-A-3 455 838
D2: EP-A-0 901 786
D3: WO-A-99 01 214
D4: GB-A-2229 364

(b) The documents **D1**, **D2**, **D3** and **D4** were not cited in the international search report. Document **D1** is cited on page 2, lines 15-23 of the present description; **D3** is equivalent to **NL-C-1 006 444** cited on page 2, lines 4-14 in the present description. Copies of **D1, D2, D3** and **D3** were appended to the written opinion.

(c) In the following arguments, page or column A, lines B to C will be cited as A/B-C.

2. Preliminary remarks

Unclear and relative terms in the claims "prevent the invention from being unambiguously distinguished from the prior art ..." (PCT Examination Guidelines, III-4.5 and 4.5a).

The term "not or poorly soluble in water" inserted in **claim 1** is such an unclear and relative term since there is no clear cut boundary between "poorly soluble" and "readily soluble". Furthermore, the solubility of polysaccharides in water is highly dependent on temperature so that a certain polysaccharide may be readily soluble in cold water but almost insoluble in hot water.

Present **claim 1** does, however, not clearly specify the degree of solubility and the temperature at which it is to determined.

Therefore, this feature was not taken into account when assessing novelty and inventive step.

3. Novelty

(a) Document **D1** discloses a method for encapsulating water-insoluble substances by

(1) dispersing an acid ester of dextrinised starch with a substituted dicarboxylic acid in water,

(2) emulsifying the water-insoluble substance in said dispersion and drying the emulsion, e.g. by spray drying (see claims 1 and 4).

In the examples, the ester of dextrin with octenyl succinic acid was dispersed in water, lemon oil (examples I to III) was emulsified therein, and the emulsion thus formed was spray dried.

(b) Octenyl succinic acid forms "an ester group derived from carboxylic acid having from 1 to 18 carbon atoms" when reacted with dextrin.

(c) Lemon oil is a fragrance.

(d) The subject-matter of **claims 1, 2** (see the temperature difference indicated at 5/30-32), **3, 9-12** (spray drying is a very common method for drying polymer dispersions), **14, 15** (see 2/18-21), **and 16** is not novel in view of **D1**.

4. Inventive step

(a) The subject-matter of **claims 4 to 8, 13 and 17** is not disclosed in **D1** or any other other cited document. It is thus novel.

(b) The additional features of the following claims are, however, obvious in view of the following parts of the literature cited:

Claim 4: **D2**, 11/45-12/22;

claims 5 to 7: **D3**, claims 1, 2 and 11 and the examples;

claim 8: **D4**, test example 2 on page 19, where a gas is absorbed on a cellulose acetate fibre.

claim 13: **D3**, claim 14.

Consequently, the subject-matter of **claims 4 to 8 and 13** is not based on an inventive step.

(c) Document **D1** discloses at 2/18-21 the use of the encapsulated products in "..., soaps, detergents, bleaches and cleansers." Such compositions are normally used for reducing odours (such as those caused by sweat). Therefore, the subject-matter of **claim 17** is not based on an inventive step.

CLAIMS

1. A method for immobilizing an active substance, wherein a mixture is prepared of the active substance and a carrier material in a liquid phase, whereafter the liquid phase is converted to a solid phase, the carrier material being an esterified polysaccharide.

2. A method according to claim 1, wherein the liquid phase is obtained by mixing and heating the active substance and the carrier material until a homogeneous liquid mixture is obtained, and wherein the solid phase is obtained by cooling.

3. A method according to claim 1, wherein the liquid phase is obtained by dissolving or dispersing the active substance and the carrier material in a solvent, and wherein the solid phase is obtained by evaporating the solvent.

4. A method according to claim 3, wherein the solvent is selected from the group of acetone, dichloromethane, diethyl ether, ethanol, methanol and isopropanol.

5. A method according to claims 1-4, wherein the liquid phase is emulsified in a liquid and wherein small particles are formed of the immobilized active substance by evaporating the liquid.

6. A method according to claim 5, wherein the liquid is water.

7. A method according to claim 1, wherein the liquid phase is a double emulsion, which is formed by preparing an oil-in-water emulsion of the active substance in a first hydrophobic phase and a solution or suspension of the carrier material in an aqueous starch solution or starch dispersion and including this oil-in-water emulsion in a second hydrophobic phase, and wherein the solid phase is formed by crosslinking the starch and removing the second hydrophobic phase.

8. A method for immobilizing an active substance, wherein the active substance is contacted in gaseous form with a carrier material in solid

phase or a liquid phase, the carrier material being an esterified polysaccharide.

9. A method according to any one of the preceding claims, wherein the esterified polysaccharide is an esterified starch, cellulose, alginate, pectin, or a derivative thereof.

10. A method according to any one of the preceding claims, wherein the polysaccharide is esterified with an acetate group, a propionate group, a butyrate group, an alkyl succinate group, wherein the alkyl group contains from 1 to 16 carbon atoms, a benzoate group, or an ester group which is derived from a carboxylic acid having 1 to 18 carbon atoms.

11. A method according to any one of the preceding claims, wherein the polysaccharide has a degree of substitution (DS) between 0.05 and a DS corresponding to a virtually complete substitution.

12. A method according to any one of the preceding claims, wherein the active substance is selected from the group of medicines, plant protection agents, paramagnetic substances, catalysts, organic reactants, cosmetic active substances, colorants, fragrances, flavors, and nutrients.

13. A method according to any one of the preceding claims, wherein the immobilized active substance is formed into a powder.

14. A method according to any one of the preceding claims, wherein the immobilized active substance is processed by the use of polymer shaping techniques, such as extrusion, injection molding, pressing or vacuum drawing.

15. A method according to any one of the preceding claims, wherein a physical or chemical modification is performed on the surface of the immobilized active substance.

16. An immobilized active substance obtainable by a method according to any one of the preceding claims.

17. Use of an immobilized active substance according to claim 16 in a detergent, fabric softener, cleaning agent, soap, shampoo, fabric conditioner,

fabric spray, ironing aid, tumble dryer addition, optical whitener, odor masking agent, personal care product, fertilizer, food, flavor, pharmaceutical, tissue, cosmetics, soil improvers, plant protection agents, covering layer or coating, paint, ink, in organic synthesis, diagnostics or agriculture.

18. Use of an esterified polysaccharide for fixing or immobilizing an active substance.

19. Use according to claim 18, wherein the active substance is an odorous substance.

20. Use according to claim 19 for reducing an odor.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
P49634PC00		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/NL 00/ 00603	30/08/2000	30/08/1999
Applicant		
PFW AROMA CHEMICALS B.V.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
P[redacted]L 00/00603

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A01N25/24 A61K7/46 C08L1/10 C08L3/06 C11D3/50
D06M15/11 B01J20/26 B01J13/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 512 693 A (DELTA BIOTECHNOLOGY LTD) 11 November 1992 (1992-11-11) page 3, line 51 -page 4, line 9 ---	1-20
X	US 4 230 687 A (SAIR LOUIS ET AL) 28 October 1980 (1980-10-28) the whole document ---	1-20
X	WO 92 11083 A (REDDING BRUCE K JR) 9 July 1992 (1992-07-09) page 11, line 7 -page 12, line 15; table 2 --- -/--	1-20

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 December 2000	27/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Reedijk, A

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]NL 00/00603

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 81, no. 22, 2 December 1974 (1974-12-02) Columbus, Ohio, US; abstract no. 140875m, page 289; XP002137793 abstract & JP 49 062623 A (FUJI PHOTO FILM) 18 June 1974 (1974-06-18)	1-7,9-16
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/NL 00/00603

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0512693 A	11-11-1992	AT 194082 T	15-07-2000
		AU 655016 B	01-12-1994
		AU 1589192 A	17-11-1992
		AU 691196 B	14-05-1998
		AU 7448394 A	22-12-1994
		CA 2083260 A	11-10-1992
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		EP 0681843 A	15-11-1995
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		FI 925600 A	09-12-1992
		WO 9218164 A	29-10-1992
		GB 2260745 A,B	28-04-1993
		HK 1006538 A	05-03-1999
		HU 62805 A	28-06-1993
		IL 101564 A	20-06-1999
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		US 6022525 A	08-02-2000
		US 5518709 A	21-05-1996
		ZA 9202636 A	30-12-1992
US 4230687 A	28-10-1980	NONE	
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		BR 8807221 A	17-10-1989
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		NO 892149 A	21-07-1989
		WO 8902814 A	06-04-1989
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		CN 1039540 A	14-02-1990
		ES 2013874 A	01-06-1990
		GR 89100195 A	31-01-1990
		IL 89526 A	01-12-1992
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		PT 90081 A	10-11-1989
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